

Exhibit 1

**EXPERT REPORT
DAVID KESSLER, M.D.**

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PART A: QUALIFICATIONS AND SCOPE

I. QUALIFICATIONS

1. My name is David A. Kessler, M.D. I received my M.D. degree from Harvard Medical School in 1979 and my J.D. degree from the University of Chicago Law School in 1978.

2. I did my pediatrics training at Johns Hopkins Hospital.

3. I was appointed in 1990 by President George H. W. Bush as Commissioner of the United States Food and Drug Administration (“FDA”) and was confirmed by the United States Senate. I also served in that position under President William Jefferson Clinton until February 1997.

4. I have taught food and drug law at Columbia University Law School, and I have testified many times before the United States Congress on food, drug, and consumer protection issues under federal and state law. Over the last thirty years, I have published numerous articles in legal, medical, and scientific journals on the federal regulation of food, drugs, and medical devices. I have had special training in pharmacoepidemiology at Johns Hopkins Hospital. My resume, including a list of my published books and articles, is included in Appendix A. A list of cases in which I have appeared as a witness, and documentation of my expert witness fee, is attached as Appendix B.

5. As Commissioner, I had ultimate responsibility for implementing and enforcing the United States Food, Drug, and Cosmetic Act. I was responsible for overseeing five Centers within the FDA. They included, among others, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health and the Center for Biologics Evaluation and Research. In addition to those duties, I placed high priority on getting promising therapies for serious and life-threatening diseases to patients as quickly as possible. During my tenure as Commissioner, the FDA announced a number of new programs including: the regulation of the

marketing and sale of tobacco products to children; nutrition labeling for food; user fees for drugs and biologics; preventive controls to improve food safety; measures to strengthen the nation's blood supply; and the MEDWatch program for reporting adverse events and product problems involving both drugs and devices. I created an Office of Criminal Investigation within the Agency to investigate suspected criminal violations of the Food, Drug, and Cosmetic Act, FDA regulations, and other related laws. I worked closely with and was ultimately responsible for the FDA's Division of Drug Marketing, Advertising and Communications. I have published articles on drug promotion and marketing practices.¹ I have likewise written extensively on the issue of addiction and have been heavily involved in the science of addiction since investigating and regulating nicotine-containing tobacco products while at FDA.

6. I am a senior advisor to TPG Capital, a leading global private equity firm, which owns pharmaceutical and biomedical companies. I previously served on the board of Aptalis Pharma and Tokai Pharmaceuticals, and I currently serve on the board of the medical device and biologics company Immucor, Inc. In these advisory and fiduciary capacities, I have advised companies on the standards and duties of care in the pharmaceutical and medical device industry. I also previously chaired the compliance committees of Aptalis, and I currently chair the quality committee of Immucor, which involves ensuring compliance with FDA laws and requirements.

7. Listed in Appendix C are documents I accessed independently from various sources, including but not limited to the FDA's website and the relevant discovery databases, and documents that have been provided to me by counsel. At my request, Appendix C was prepared

¹ These include: Kessler, D. (1990). The federal regulation of prescription drug advertising and promotion. JAMA 264:2409-15); Kessler, D. (1991). Drug promotion and scientific exchange. The role of the clinical investigator. N Engl J Med 325:201-3; Kessler, D. (1991). Communicating with patients about their medications. N Engl J Med 325:1650-2; Kessler, D. Therapeutic-class wars--drug promotion in a competitive marketplace. N Engl J Med 331:1350-3; Kessler, D. (2007). Direct-to-consumer advertising: is it too late to manage the risks? Ann Fam Med 5:4-5.

by counsel. Based on my review of those documents and my training and experience, I have a number of opinions that are detailed below.

8. The causes of action in this litigation include: public nuisance; negligence; common law fraud; civil conspiracy; violation of the Racketeer Influenced and Corrupt Organizations (“RICO”) Act; violation of consumer protection laws; and unjust enrichment.

9. It is my understanding that the plaintiffs include: County of Cuyahoga and County of Summit.

10. Likewise, it is my understanding that the defendants in this action are as follows: Actavis LLC, Actavis Pharma, Inc., Allergan Finance LLC, Allergan PLC, AmerisourceBergen Drug Corporation, ANDA, Inc., Cardinal Health, Inc., Cephalon, Inc., CVS Indiana, LLC, CVS Rx Services, Inc., Discount Drug Mart, Inc., Endo Health Solutions Inc., Endo Pharmaceuticals, Inc., H.D. Smith Holding Company, H.D. Smith Holding Company (County of Cuyahoga Only), H.D. Smith Holdings LLC, H.D. Smith Holdings, LLC (County of Cuyahoga Only), H.D. Smith LLC d/b/a H.D. Smith, H.D. Smith, LLC d/b/a H.D. Smith (County Of Cuyahoga Only), HBC Service Company, Health Mart Systems, Inc., Health Mart Systems, Inc. (County of Cuyahoga only), Henry Schein Medical Systems, Inc., Henry Schein Medical Systems, Inc. (County of Summit only), Henry Schein, Inc., Henry Schein, Inc. (County of Summit only), Insys Therapeutics, Inc., Janssen Pharmaceuticals, Inc., Johnson & Johnson, Mallinckrodt LLC, Mallinckrodt PLC, McKesson Corporation, Miami-Luken, Inc., Noramco, Inc., Par Pharmaceutical Companies, Inc., Par Pharmaceutical, Inc., Prescription Supply, Inc., Purdue Pharma, Inc., Purdue Pharma, L.P., Rite Aid of Maryland, Inc. d/b/a Rite-Aid Mid-Atlantic Customer Support Center, Inc., Specgx LLC, Teva Pharmaceutical Industries, Ltd., Teva

Pharmaceuticals USA, Inc., The Purdue Frederick Company, Inc., Walgreen Co., Walgreen Eastern Co., Walmart Inc., Watson Laboratories, Inc.

11. The opioid products discussed in this report include: OxyContin (Purdue), OxyContin Reformulated (Purdue), MS Contin (Purdue), Opana ER (Endo), Opana ER reformulated (Endo), Percocet (Endo), Duragesic (Janssen), Nucynta IR (Janssen), Nucynta ER (Janssen), Actiq (Teva), Fentora (Teva), Kadian (Actavis), Exalgo (Mallinckrodt), Xartemis ER (Mallinckrodt), and generic OxyContin (Mallinckrodt).

II. SCOPE

12. I have been asked by counsel for the plaintiffs to discuss drug sponsor obligations under standards provided under United States food and drug laws, regulations, guidances, and industry practice as they pertain to prescription opioids, and to discuss the purposes of those obligations and standards and the effect, if any, that any departures from those standards would be expected to have on the use, misuse and abuse of prescription opioids during the past two decades or so. I have also been asked to review the discovery records of specified defendant opioid manufacturers² for the purpose of formulating an opinion as to whether any one or more of those manufacturers departed from accepted drug regulatory standards and, if so, to describe how.³

² As used throughout this report, the term "manufacturer" refers to a sponsor of a drug.

³ The following Schedules are attached to this Report:

Schedule 1 contains general information about the drugs that are the subject of this Report.

Schedule 2 contains the approval dates of various dosages of the drugs that are the subject of this Report.

Schedule 3 contains a Morphine Milligram Equivalent (MME) conversion table.

Schedule 4 contains definitions of addiction and related terms.

Schedule 5 contains a list of Defendants and Plaintiffs in this MDL.

Schedule 6 contains relevant communications from FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC).

Schedule 7 contains relevant FDA Advisory Committee materials.

Schedule 8 contains IMS sales data for the drugs that are the subject of this Report. I understand from counsel that this Schedule has been prepared by Greylock McKinnon Associates.

Schedule 9 contains FDA's Risk Evaluation and Mitigation Strategies (REMS) requirements for oral opioids.

PART B: STANDARDS

III. RESPONSIBILITIES UNDER THE FOOD DRUG AND COSMETICS ACT

13. FDA is a public health, consumer protection agency. The agency regulates not only the approval of prescription drugs but also their marketing and promotion. The principles in FDA's regulation of marketing and promotion help (1) assure that consumers can make informed choices with their doctors about the use of medicines by being able to weigh the risks and benefits; (2) prevent the exposure of patients to potentially serious and avoidable health risks; (3) assure that medicines are used safely; and (4) prevent the inappropriate prescription (e.g., incorrect treatment choice, over or under prescription of the drug, etc.).

14. According to the Food Drug and Cosmetic Act ("FDCA" or "the Act"), FDA has jurisdiction over prescription drug labeling.

15. The Act defines label to mean "a display of written, printed, or graphic matter upon the immediate container of any article ..." ⁴ According to FDA regulations, "Label means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity." ⁵ The Act defines labeling to mean "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." ⁶ Similarly, FDA regulations provide that labeling includes "all

Schedule 10 contains FDA's REMS requirements for Transmucosal Immediate Release Fentanyl.
Schedule 11 contains relevant sales representative call notes for drugs that are the subject of this Report.
Schedule 12 contains chronologies of relevant changes to the labels of the drugs that are the subject of this Report.
All Schedules other than Schedule 8 were prepared by legal staff under my direction and subject to my review.

⁴ 21 U.S.C. § 321(k) (2016).

⁵ 21 CFR § 1.3(b) (2018).

⁶ 21 U.S.C. 321(m) (2016).

written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.”⁷

16. FDA generally describes labeling as comprising two types: (1) the label and (2) promotional labeling.

17. Promotional labeling includes statements and materials issued by, on behalf of, or with the involvement of a drug sponsor or manufacturer.

18. Promotional labeling shapes what healthcare providers and consumers understand about a drug—its safety, efficacy, and how to use it.

19. The key principles in FDA’s regulation of marketing and promotion include the following:

A. Information About a Drug Must Be Truthful

20. Promotional labeling must not be false or misleading. Under FDA regulations, certain types of statements are considered to be “false or misleading,” such as:

- “Contains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is better, more effective, useful in a broader range of conditions or patients ..., safer, has fewer, or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience...”⁸
- “Contains a drug comparison that represents or suggests that a drug is safer or more effective than another drug in some particular when it has not been demonstrated to be safer or more effective in such particular by substantial

⁷ 21 CFR § 1.3(a) (2018).

⁸ 21 CFR § 202.1(e)(i) (2018). The FDA has applied this standard to quality of life and patient preference claims as well. *See, e.g.,* DDMAC Letter to GlaxoSmithKline re FLONASE, May 9, 2007.

evidence or substantial clinical experience.”⁹

- “Contains a representation or suggestion that a drug is safer than it has been demonstrated to be by substantial evidence or substantial clinical experience, by selective presentation of information from published articles or other references that report no side effects or minimal side effects with the drug or otherwise selects information from any source in a way that makes a drug appear to be safer than has been demonstrated.”¹⁰

21. The Act states that whether a drug’s labeling or advertising is misleading should take into account “not only representations made or suggested” but also “the extent to which the labeling or advertising fails to reveal facts material in light of such representation.”¹¹

22. The importance of truthful and non-misleading information in promotional materials is underscored by FDA stating:

FDA believes it is critically important to disclose risk information in prescription drug and medical device promotion appropriately and effectively to healthcare professionals and consumers. This information helps consumers know whether drugs or devices may be appropriate for them as well as what they should tell their healthcare professionals about before taking or using or while taking or using a product. It also lets consumers know what risks they might experience and what steps they need to take for safety reasons (e.g., no driving) because of taking or using a product. Appropriate risk disclosures help healthcare professionals by giving them some of the information they need to know about the product that will enable them to safely use or prescribe it.¹²

⁹ 21 CFR § 202.1(e)(ii) (2018).

¹⁰ 21 CFR § 202.1(e) (iv) (2018).

¹¹ 21 U.S.C. § 321(n) (2016).

¹² FDA, Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion at 5-6 (May 2009).

B. The Risks and Benefits of a Drug Must Be Presented in a Balanced Fashion

23. With respect to promotional materials, manufacturers must “present a fair balance between information relating to the side effects and contraindications and information relating to the effectiveness of the drug.” FDA explains fair balance as follows: “The law requires that product claim ads give a ‘fair balance’ of information about drug risks as compared with information about drug benefits. This means that the content and presentation of a drug’s most important risks must be reasonably similar to the content and presentation of its benefits.”¹³

24. In a draft guidance, FDA stated,

Although the regulations [regarding fair balance, disclosure of risks, and similar matters] were promulgated in the context of prescription drug advertising, the guidance they provide on what FDA considers false or misleading in promotion has broader applicability. For example, promotional pieces that fail to present a balanced view of the risks and benefits of a product are generally considered to be false or misleading and also generally fail to reveal material facts about the product being promoted. Because both labeling pieces for drugs and devices, and advertising pieces for prescription drugs and restricted devices, are considered to misbrand a product if they are false or misleading or fail to reveal material facts, drug and device manufacturers should take into account the guidance provided by these regulations when promoting a drug.¹⁴

C. Promotional Statements Need to Be Supported by Substantial Evidence

25. Under United States food and drug laws, a drug may not be introduced into interstate commerce unless its sponsor has shown that the drug is safe and effective for the intended conditions of use as established by substantial evidence.¹⁵

26. Likewise, all product claims must be supported by substantial evidence.¹⁶

¹³ <https://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072025.htm#F>

¹⁴ FDA, Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion at 12 (May 2009).

¹⁵ 21 U.S.C. § 321 (2016).

¹⁶ 21 C.F.R. § 201.1(e)(4)(ii)(b) and (c) (2018).

27. The law requires that “adequate and well-controlled investigation” be used to demonstrate a drug’s safety and effectiveness,¹⁷ and the FDA has typically required that substantial evidence consist of at least two adequate and well-controlled clinical trials.¹⁸

D. New Safety Information Must Be Conveyed Upon Receipt to Inform Healthcare Providers and Patients About New Safety Risks

28. Generally, a drug manufacturer has responsibility to update the label and labeling upon receipt of evidence that suggests a reasonable possibility of a causal association between a drug and an adverse event.

29. Procedural mechanisms exist under FDA regulations whereby a drug manufacturer can make changes to the label and labeling called “Changes Being Effected.”¹⁹

30. As FDA stated in 1979, nothing in the Act prohibits a manufacturer from warning healthcare providers and consumers about important safety risks.²⁰

31. The approval of a drug at one point in time does not relieve a drug manufacturer from the responsibility to update and convey important safety information to healthcare providers and patients.

¹⁷ 21 U.S.C. § 355(d) (2018).

¹⁸ FDA, Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biologic Products at 4 (May 1998).

¹⁹ See 21 CFR 314.70; FDA, *Guidance for Industry: Changes to an Approved NDA or ANDA* (April 2004). Pharmaceutical drug manufacturers must make reports to the FDA, including Annual Reports that provide a “Summary” section that includes “A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product.” 21 C.F.R. 314.81(b)(2)(i). The Summary section “is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information” *Id.* Holders of abbreviated applications must also make such Annual Reports for each of its approved abbreviated applications. 21 C.F.R. 314.81(b); see, e.g., 3/25/29 Dep. of Scott Tomskey, and Exhs. 7, 11 and 13 (FDA generic opioid ANDA approvals referencing sections 314.80, 314.81 and 314.98).

²⁰ 44 Fed. Reg. 37434, 37447 (1979). Drug manufacturers may communicate safety information contained in the label through, for example, a “Dear Doctor” letter or other communication. 21 C.F.R. 201.100(d)(1).

32. The Act prohibits the delivery for introduction, and causing the delivery for introduction, into interstate commerce of a misbranded drug.²¹ A person who misbrands a drug with the intent to defraud or mislead is guilty of a felony offense.²²

E. Drug Manufacturers Cannot, Under the Guise of Sponsoring Medical Education, Convey Misleading Promotion

33. As I have written previously, the type of medical education activities that a drug manufacturer may engage in depends on whether such activities are considered “educational” or “promotional.” FDA’s drug regulations draw a critical distinction between “scientific exchange” and “promotional activities.” While the promoting or advertising of investigational drugs is prohibited, the Agency recognizes that educational exchanges among scientists regarding drugs prior to approval has scientific value. When a pharmaceutical firm supports these educational activities, however, the line between “education” and “promotion” becomes harder to draw. The distinction is obviously important to pharmaceutical firms because FDA regulates promotional activities under its prescription drug labeling and advertising regulations. Although educational activities sponsored by the manufacturer may be considered by FDA as labeling, FDA has generally exercised its discretion not to enforce that authority with respect to purely educational activities.²³

34. The criteria to distinguish educational from promotional activities include the degree to which a program is “independent” of the drug company.²⁴ “The more directly involved a company is, the more concerned FDA becomes about its promotional dimensions. Long-term

²¹ 21 U.S.C. § 331(a) (2012).

²² 21 U.S.C. § 331(a)(2) (2012).

²³ See generally Kessler DA & Pines WL. The Federal Regulation of Prescription Drug Advertising and Promotion. *JAMA* 1990; 264(18): 2409-2415.

²⁴ *Id.* at 2411.

or ongoing financial relationships between the speakers and the company will tilt the FDA's judgment toward the category of promotional activities.²⁵

35. In 1997, FDA published guidance for the industry on the proper limits of corporate sponsorship, distinguishing between “(1) Activities (programs and materials) performed by, or on behalf of, the companies that market the products; and (2) activities, supported by the companies, that are otherwise independent from the promotional influence of the supporting company.”²⁶ According to FDA:

In determining whether an activity is independent of the substantive influence of a company, the agency examines whether and to what extent the company is in a position to influence the presentation of information related to its products or otherwise transform an ostensibly independent program into a promotional vehicle. FDA is concerned that companies may influence the content of educational programs both directly and indirectly. Directly, by being involved in the selection of speakers or in the treatment of topics. Indirectly, through the nature of the relationship between the company and the provider (e.g., if the provider has reason to believe that future financial support from the company depends upon producing programs that promote the company's products).²⁷

F. Promotional Information Needs to Be Evaluated by the Totality of the Impression it Creates

36. As FDA has stated in industry guidance regarding the presentation of risk information in prescription drug promotion:

It is important to emphasize that when FDA evaluates the risk communication in a promotional piece, FDA looks not just at specific risk-related statements, but at the *net impression* – i.e., the message communicated by all elements of the piece as a whole. The purpose of the evaluation is to determine whether the piece *as a whole* conveys an accurate and non-misleading impression of the benefits and risks of the promoted product. Manufacturers should therefore focus not just on individual claims or presentations, but on the promotional piece as a whole. A promotional communication that conveys a deceptive net impression of the

²⁵ *Id.*

²⁶ FDA, Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64074-101 (Dec. 3, 1997).

²⁷ *Id.* at 094-096.

product could be misleading, even if specific individual claims or presentations are not misleading.²⁸

G. Drug Manufacturers May Not Promote Unapproved or Off-Label Uses

37. It is not a drug, by itself, that is regulated or that receives approval. It is a drug for an “intended use” that is reviewed and approved by FDA. Thus, it is not a chemical compound that is approved, but a chemical compound for a specific disease or condition at a specific dose that FDA reviews and approves.

38. Drugs that are promoted for uses that have not been approved by FDA have long been held to be misbranded under the Act.²⁹

39. FDA has voiced serious concerns regarding the promotion of drugs for non-approved uses. These concerns stem from the fact that the Agency has not reviewed and approved the indications for which the drug is being used.³⁰

40. Promotion of drugs for unapproved uses may put patients at risk. FDA has not reviewed or assured the safety or efficacy of the drug for unapproved uses. Moreover, promotion for unapproved uses may increase the number of patients exposed to the drug’s risks.

H. Promotional Activities Are Recognized to Influence the Prescriber

41. Disclosure of risk information in promotional materials is important because drug promotion strongly influences prescribing behavior. As noted by the World Health Organization

²⁸ FDA, Draft Guidance for Industry- Presenting Risk Information in Prescription Drug and Medical Device Promotion (May 2009) at 7.

²⁹ 21 U.S.C. § 352(f)(1) (2012).

³⁰ Testimony on Unapproved Uses of Prescription Drugs, Before the S. Comm. on Labor and Human Resources, 103rd Cong. 5 (February 22, 1996) (statement of William B. Schultz, FDA Deputy Commissioner for Policy).

in a 2002 report regarding drug promotion, “[c]ompany funding of doctors, of educational events and of research are important elements in this influence.”³¹

42. Doctors, however, typically underestimate this influence.³² As a group, we physicians like to believe that our judgment and dedication to our patients is unclouded by pharmaceutical company influences.

43. A study quoted by the World Health Organization in its 2002 report found that “reliance on information provided by the pharmaceutical industry was negatively associated with prescribing rationality. That is, doctors who relied on promotional information wrote less rational prescriptions for the case studies than those who reported relying less on promotion.”³³

I. Drug Manufacturers Have a Responsibility to Engage in the Dissemination of Information in Order to Minimize Risks

44. In 2007, the Act was amended to provide the Agency the authority to require a drug company to develop and comply with a Risk Evaluation Mitigation Strategy (REMS) for a drug for which there is a serious risk of an adverse drug experience.³⁴ REMS provide additional interventions beyond FDA-approved labeling that are necessary to ensure that the drug’s

³¹ Norris P, *Drug Promotion: what we know, what we have yet to learn*, World Health Organization and Health Action International at 73 (2005), available: http://www.who.int/medicines/areas/rational_use/drugPromodhai.pdf.

³² Reynolds E., et al. (2018). Reconciling a “pleasant exchange” with evidence of information bias: A three-country study on pharmaceutical sales visits in primary care. *Health Policy* 122:250-55.

³³ Norris P, *Drug Promotion: what we know, what we have yet to learn*, World Health Organization and Health Action International at 37 (2005), available: http://www.who.int/medicines/areas/rational_use/drugPromodhai.pdf; see also Alves T., et al. (2018). Medicines Information and the Regulation of the Promotion of Pharmaceuticals. *Sci Eng Ethics* doi:10.1007/s11948-018-0041-5; Fickweiler F., et al. (2017). Interactions between physicians and the pharmaceutical industry generally and sales representatives specifically and their association with physicians’ attitude and prescribing habits: a systematic review. *BMJ Open* doi:10.1136/bmjopen-2017-016408; Brax, H., et al. (2017). Association between physicians’ interaction with pharmaceutical companies and their clinical practices: a systematic review and meta-analysis. *PLoS One* 12:e0175493; DeJong, C. et al. (2016). Pharmaceutical industry-sponsored meals and physician prescribing patterns for medicare beneficiaries. *JAMA Internal Medicine* 176: 1114–1122.

³⁴ 21 U.S.C. 355-1(a)(1) (2018).

benefits outweigh its risks.³⁵ Under the Act, failure to comply with a REMS requirement renders the drug misbranded and allows for imposition of civil penalties.³⁶

45. A REMS may consist of a Medication Guide, a Patient Package Insert, or a Communication Plan,³⁷ and must include assessments and a timetable for submissions of REMS assessments.³⁸

46. FDA may also require Certain Elements to Assure Safe Use (ETASU), such as certification and/or specialized training of prescribers; certification of pharmacies or other dispensers; dispensing/administration only in certain health care settings e.g., hospitals; dispensing/administration only with evidence of safe-use conditions; requiring each patient to be subject to certain monitoring; or enrollment of treated patients in registries.³⁹

47. A responsible manufacturer whose drug requires a REMS would ensure compliance with the REMS.

48. Prior to REMS, FDA approved a small number of drugs with risk minimization action plans (RiskMaps) or required a RiskMap post-approval.⁴⁰ RiskMaps were developed for drugs, including certain opioids, that required risk management strategies beyond their FDA-approved labeling.

49. FDA's 2005 Guidance for industry, *Development and Use of Risk Minimization Actions Plans*, provided manufacturers with guidance on designing RiskMaps to minimize

³⁵ See 21 U.S.C. 355-1(a) (2018).

³⁶ See 21 U.S.C. 331(d) (2012); 21 U.S.C. 333 (2017).

³⁷ See 21 U.S.C. 355-1(e)(2)-(3) (2018).

³⁸ See 21 U.S.C. 355-1(d) (2018).

³⁹ See 21 U.S.C. 355-1(f)(3) (2018).

⁴⁰ FDA, Guidance for Industry: Development and Use of Risk Minimization Action Plans (2005) at 4-7, *available at* <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071616.pdf>

identified risks, selecting tools to minimize those risks, evaluating RiskMaps and monitoring tools, and communicating with FDA about RiskMaps.⁴¹

50. A responsible manufacturer whose drug was approved with a RiskMap must ensure that it maintains an effective RiskMap in order to minimize the risks identified in the RiskMap.

J. The Manufacturer of a Drug Has Primary Responsibility for a Drug's Safety and its Promotional Information

51. FDA regulation of a drug cannot anticipate and protect against all safety risks to individual consumers. Even the most thorough regulation of a product may fail to identify potential problems presented by the product.

52. In addition, the duties of a drug company are based not only on FDA laws and regulations, but also on the risks presented by a drug about which the company knew, should have known, or should have investigated.

53. A drug company has a responsibility, independent of what FDA directs it to do, to alert physicians and patients to risks that were unknown to or poorly understood by FDA, but were known to the company. This duty predates by decades the advent of federal regulation of drugs. *See, e.g., Thomas v. Winchester*, 6 N.Y. 397 (1852).

54. Manufacturers have superior resources that are or should be committed to overseeing the safety of the drugs they market and their promotional materials. As a result, manufacturers invariably get safety information before FDA does and have access to information that is not available to FDA. Company scientists and physicians also develop impressions and understanding of a drug's potential safety profile that may be more informed than FDA's.

⁴¹ *Id.* at 9-16.

55. Thus, what a drug company knows about a drug and what the FDA knows may be different.

K. Deviations from or Non-Conformance with FDA Requirements on Marketing and Promotion Puts Consumers at Risk

56. False or misleading promotion about drugs deprives healthcare providers and consumers of vital information that informs decision making and can thus puts consumers at risk.

57. There is a long history of FDA concerns about understatement of risks, overstatement of benefits, promotion for unproved uses, and non scientifically supported superiority claims.

58. Inappropriate marketing and promotion can result in an increase in prescribing, an inappropriate use of prescription drugs, inadequate medical care, and put consumers at increased risks.

59. When a drug has addictive properties, inappropriate marketing can result in an increase in prescribing, an inappropriate use of prescription of drugs, and an increase in the risk that the drug may be abused or cause addiction, and in increase in the risk of inadequate medical care.⁴²

L. Corrective Marketing May Be Used to Counteract Misleading Information About a Drug's Risks and Benefits.

60. As discussed above, FDA regulations require that promotion of a prescription drug contain accurate information about the drug's benefits and risks.

⁴² Hadland et al. (2019). Association of Pharmaceutical Industry Marketing of Opioid Products With Mortality From Opioid-Related Overdoses. JAMA Netw Open. 2:e186007.

61. If serious risks about a drug are not disclosed or if false or misleading information is disseminated, corrective promotion can be used to counteract these erroneous statements.⁴³

62. Research has demonstrated that corrective promotion can be effective in countering false and misleading statements made about prescription drug products.⁴⁴

63. In 2009, FDA required Bayer HealthCare Pharmaceuticals to produce and air a corrective media plan for Yaz, a birth control pill, in response to two of Bayer's advertisements for the drug that were "misleading because they broaden the drug's indication, overstate the efficacy of Yaz, and minimize serious risks associated with the use of the drug. Thus, the TV ads misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act"⁴⁵

64. FDA's letter to Bayer stated that the "violations are concerning from a public health perspective because they encourage the use of Yaz in circumstances other than those in which the drug has been approved, over-promise the benefits, and minimize the risks of Yaz."⁴⁶

⁴³ See, e.g., FDA Warning Letter to Bayer Pharmaceuticals re Yaz Tablets, Oct. 3, 2008.

⁴⁴ See <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090276.htm> ("Regarding exposure to corrective advertising, we found that a corrective ad counteracted beliefs of an overstatement of efficacy claim, but was less successful in counteracting omission of risk. Corrective ad exposure also affected perceptions of, and intended behaviors toward, the drug. Examining the effect of similarity and time delay suggests corrective ad exposure can influence consumer perceptions of drug efficacy, risks, and benefits previously established by violative ads. Corrective ads also can weaken consumer intentions to consider and seek more information about a drug. However, ad similarity does not appear to affect consumer perceptions and preferences. The length of the delay between violative and corrective ad exposure has limited influence. Broadly, these results offer evidence in support of the contention that television advertising explicitly designed to correct viewer beliefs about the risks and benefits of a prescription drug can be successful, and while further research is needed, these findings suggest that corrective advertising appears to be a viable remedy to combat some forms of misinformation through advertising.").

⁴⁵ *Id.*

⁴⁶ *Id.* FDA has sent similar letters to manufacturers when it found that their promotional materials misbranded a drug within the meaning of the FD&C Act and corrective messaging was warranted. See, e.g., FDA July 27, 2015 letter to ECR Pharmaceuticals re TussiCaps ("Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective message about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional piece(s) and/or activity and focus on the corrective message(s), OPDP recommends that corrective piece(s) include a description of the violative promotional pieces

65. To the counter the serious violations identified in FDA's warning letter, FDA requested that Bayer submit "a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional material."⁴⁷

66. In compliance with FDA's request, Bayer paid \$20 million to run a promotional campaign that told consumers that Yaz should not be taken for the inappropriate off-label uses that Bayer had promoted.⁴⁸

and/or activity, include a summary of the violate message(s), provide information to correct each of the violative message(s), and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated."); FDA Letter to Duchesnay re Diclegis delayed-release Tablets, Aug. 7, 2015, *available at* <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM457961.pdf> ("Because the violations described above are serious and repeated, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials.")

⁴⁷ In January 2003, FDA sent a letter to Purdue requesting that it cease disseminating advertisements for OxyContin that minimized risks, overstated the efficacy of and omitted important information about the indication for OxyContin. ENDO-OPIOID_MDL-03006241 at 32. In addition, FDA requested that Purdue provide a plan of corrective action to address these promotional violations. *Id.* In response, Purdue issue a corrective advertisement, "which called attention to the warning letter and the cited violations and directed the reader to the prominently featured boxed warning and indication information for OxyContin." *Id.* "According to FDA, the corrective advertisement ran for 3 months and appeared in approximately 30 medical journals." *Id.* at n.39.

⁴⁸ See Natasha Singer, *A Birth Control Pill That Promised Too Much*, N.Y. TIMES, Feb. 8, 2009, www.nytimes.com/2009/02/11/business/11pill.html.

PART C: THE OPIOID MANUFACTURERS' MARKETING AND PROMOTION DEVIATED FROM FDA STANDARDS, INCREASING THE RISK OF ABUSE AND ENDANGERING PATIENT SAFETY

IV. PRIOR TO THE INTRODUCTION OF OXYCONTIN, HEALTHCARE PROVIDERS EXERCISED CAUTION IN PRESCRIBING STRONG OPIOIDS

67. For most of the 20th Century, American physicians approached prescribing opioids with caution,⁴⁹ believing opioids should not be used to manage chronic pain due to lack of evidence regarding their effectiveness and the risk of addiction.⁵⁰

68. The abuse of opioids in the United States is not a new phenomenon. In 1803, Friedrich Wilhelm Adam Sertürner, a German chemist, isolated a substance from crude opium.⁵¹ He named the substance morphine.⁵² The widespread use of morphine during the American Civil War resulted in wave of opioid abuse and addiction.⁵³

69. By the 1890s, medical textbooks and instructors regularly warned against overprescribing opioids,⁵⁴ and by the early 1900s the United States government sought to end the non-medicinal use of opium.⁵⁵ In 1909, Congress passed the Opium Exclusion Act, which barred the importation of opium for the purposes of smoking.⁵⁶ The Harrison Narcotics Act of

⁴⁹ Phillips JK, Ford MA, Bonnie RJ. (2017). Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. National Academies Press, *available at*: <https://www.ncbi.nlm.nih.gov/books/NBK458661/Phillips>.

⁵⁰ *Id.*

⁵¹ *Id.*

⁵² *Id.*

⁵³ Erick Trickey, *Inside the Story of America's 19th-Century Opiate Addiction*, Smithsonian Mag (Jan. 4, 2018), <https://www.smithsonianmag.com/history/inside-story-americas-19th-century-opioids-addiction-180967673>.

⁵⁴ *Id.*

⁵⁵ *The History of Opiates*, Michael's House, <https://www.michaelshouse.com/opiate-rehab/history-of-opiates/> (last visited Sept. 21, 2018).

⁵⁶ *Id.*

1914 required physicians and pharmacists to register to distribute opium.⁵⁷ By 1930, heroin traffic had dropped substantially due to domestic and international restrictions,⁵⁸ and in order to avoid addiction, opioid prescribing was mainly limited to treating acute pain in the dying.⁵⁹

70. Oxycodone, a semi-synthetic opiate manufactured by modifying a chemical found in opium, was first introduced in 1916,⁶⁰ and in the next few decades was used mainly for acute pain.⁶¹ It became more widely available in the 1950s when the FDA approved Percodan, a mix of oxycodone and aspirin.⁶² The late 1970s and early 1980s brought the approval of additional immediate release opioids, including Percocet (oxycodone hydrochloride and acetaminophen) in 1976 and Vicodin (hydrocodone and acetaminophen) in 1983.⁶³

71. The dangers of oxycodone have been known for over 50 years. In 1960, the United Nations Office on Drugs and Crime classified oxycodone as a dangerous drug as part of The Dangerous Drugs (Amendment) Ordinance.⁶⁴ In 1961, the Attorney General of California “openly cited the need for increased control of Percodan, stressing that the drug was creating a new class of addicts composed of otherwise honest, not criminally inclined persons.”⁶⁵

⁵⁷ *Id.*

⁵⁸ *Id.*

⁵⁹ *Id.*

⁶⁰ *Id.*

⁶¹ Kalso, Eija. (2005). Oxycodone. *J Pain Symptom Manage.* 29(5 Suppl):S47-56.

⁶² *The History of Opiates*, Michael’s House, <https://www.michaelshouse.com/opiate-rehab/history-of-opiates/> (last visited Sept. 21, 2018).

⁶³ *See* <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=085106>.

⁶⁴ *Oxycodone*, www.cesar.umd.edu/cesar/drugs/oxycodone.asp (date last visited Sept. 21, 2018).

⁶⁵ *Id.*

72. In 1970, Congress passed the Controlled Substances Act (CSA).⁶⁶ The Act established five schedules that classify substances according to “how dangerous they are, their potential for abuse and addiction, and whether they possess legitimate medical value.”⁶⁷ The drugs at issue in this Report are scheduled as Schedule II drugs, meaning they have a “high potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous.”⁶⁸

73. Extended-release opioid products, such as controlled-release morphine sulfate products MS CONTIN and Kadian and controlled-release fentanyl products, were positioned as for use in limited circumstances. Nonetheless, reports and articles on the abuse of controlled release opioids began appearing within a few years of when these drugs began hitting the market in the late 1980s. In 1990, only three years after MS CONTIN was approved, an article was published highlighting the drug’s abuse potential.⁶⁹ The article noted that in areas such as Cincinnati, MS CONTIN had surpassed hydromorphone 4-mg tablets as the most abused prescription opioid.⁷⁰ A 1993 study on the abuse potential of opioids found that 85% of the addicts surveyed had used controlled-release morphine.⁷¹

⁶⁶ *DEA History in Depth 1970-1975*, DEA, <https://www.dea.gov/sites/default/files/2018-07/1970-1975%20p%2030-39.pdf> (date last visited Sept. 21, 2018).

⁶⁷ *Id.*

⁶⁸ *Drug Scheduling*, DEA, <https://www.dea.gov/drug-scheduling> (date last visited Sept. 21, 2018). Hydrocodone combination products, such as Vicodin, were originally scheduled as Schedule III drugs with moderate to low potential for physical and psychological dependence. As of October 6, 2014, hydrocodone combination products are now Schedule II drugs. Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products from Schedule III to Schedule II, 79 Fed. Reg. 163, 49661-49682 (Aug. 22, 2014), https://www.deadiversion.usdoj.gov/fed_regs/rules/2014/fr0822.htm

⁶⁹ Crews, JC, Denson DD, Recovery of morphine from a controlled-release preparation. A source of opioid abuse. *Cancer*. 1990 Dec 15;66(12):2642-4.

⁷⁰ *Id.*

⁷¹ Brookoff D, Abuse potential of various opioid medications. *J Gen Intern Med*. 1993 Dec; 8(12):688-90.

74. The lessons learned in the early 20th Century regarding the risks of opioid abuse were pushed aside by the aggressive marketing of a new generation of opioids starting in the 1990s, and opioid manufacturers' understatement of their risks and overstatement of their benefits as set forth below.

V. PURDUE

A. Overview

75. Purdue has promoted and sold various opioid products, including MS Contin and OxyContin.⁷²

76. OxyContin is oxycodone in an extended release (ER) tablet, and oxycodone is a full opioid agonist that is relatively selective for the mu receptor.⁷³

77. Purdue received initial FDA approval to market OxyContin on December 12, 1995. A discussion of subsequent labeling changes, including approval of OxyContin reformulated, is contained in Schedule 12.

78. In reviewing OxyContin, the FDA Medical Reviewer, Dr. Curtis Wright, IV, approached the review as evaluating an existing drug with a new dosage form. Oxycodone had been on the market as a stand-alone and combination drug that was administered every four to six hours. As noted in the above historical background section, the 1980s and 1990s saw the development of extended release delivery forms for a number of drug entities, including opioids. The review of the OxyContin NDA thus focused primarily on whether the twelve-hour administration was equivalent to the shorter acting immediate-release oxycodone formulation. The longest controlled clinical studies that were submitted as part of the OxyContin NDA were

⁷² Other opioid products marketed by Purdue include Butrans, Dilaudid, Dilaudid-HP, Hysingla ER, Targiniq ER.

⁷³ PPLPC018001498098 at 3.

for fourteen days.⁷⁴ Dr. Wright concluded that OxyContin was similar in efficacy and safety to immediate release oxycodone.⁷⁵

79. Notwithstanding that FDA's review primarily focused on the safety and efficacy of this new dosage formulation, Purdue engaged in a marketing and promotional strategy "to change the way pain is treated in America."⁷⁶

80. Prior to the marketing of OxyContin, certain individual healthcare providers, such as Drs. James Campbell, June Dahl, Kathleen Foley, Michael Miller, and Russell Portenoy, advocated for improved pain assessment and treatment. However, Purdue's marketing and promotion focused on expanding the market for strong opioids.⁷⁷

81. Purdue acknowledged in 2001 that its promotional activities "contributed to a paradigm shift."⁷⁸

82. This paradigm shift expanded the use of opioids in treating pain,⁷⁹ and the concomitant increase in sales of OxyContin and opioid products in general produced *ipso facto* more opioid drugs in interstate commerce.

⁷⁴ PURCHI-000667209 at 41.

CLINICAL STUDIES					
Study Name	Indication	N	Comparison	Duration	PK/PD?
<u>Controlled Trials</u>					
OC91-0402A	CANCER	57/54	CR V, IR	5 DAY + / -	
OC91-0402B	CANCER	81/83	CR V, IR	5 DAY + / -	
OC93-0202	CANCER	50	CR V, IR	7 DAY X/O	PK/PD
OC92-1102	OA	44/44/45	10,20 CR V, PLC	14 DAY	PK/PD
OC92-1201	LOW BACK	57	CR V, IR	7 DAY X/O	PK/PD
OC88-1105	POSTOP	30/30/30	10,20,30 CR	SINGLE DOSE	none
		30/31/31	IR, PLC, PCT		

⁷⁵ PURCHI-000667209 at 39, 52-53.

⁷⁶ PKY181297965 at 1.

⁷⁷ The elements of Purdue's marketing and promotion that focused on expanding the market for strong opioids were investigated and summarized by the United States General Accounting Office in 2003.

⁷⁸ PDD1503491667 at 1; *see also* PPLP003409951, PPLP003541889, PPLP004001344.

83. It is axiomatic that the more controlled substance drugs in interstate commerce, the more diversion and abuse of those drugs. Dr. Wright noted this about opioids in an article that he and other colleagues published after he left FDA and began working at Purdue.⁸⁰

84. As set forth below,⁸¹ Purdue's marketing campaign for strong opioids was extensive, misleading, and reframed the risks and benefits of not only OxyContin but opioids in general, without substantial evidence.⁸² As a result of Purdue's false and misleading promotional strategies, Purdue increased the likelihood of mis- and over-prescriptions of opioids, inadequate medical care, and the presentation of avoidable risks, such as the risk of abuse, addiction, and overdose.

⁷⁹ In Purdue meeting minutes from an April 23, 2001 meeting between Purdue and FDA, Purdue agreed that there had been a "shift in prescribing patterns" from malignant to non-malignant pain conditions, including a ten-fold increase in OxyContin prescriptions as compared to extended-release morphine:

It was noted, from 1995 to present there had been a shift in prescribing patterns out of oncology specialties into family practitioners and, when looking by indication, mentions of neoplasm were decreasing and musculoskeletal disease were increasing. Musculoskeletal disease included such terms as lumbago, myalgia and other back pain related terms. Dr. Pollock compared the number of mentions in IMS of OxyContin to MS Contin and noticed that while MS Contin prescribing had remained relatively constant, OxyContin had increased 10 fold. The Agency implied that this was a trend they were concerned with. Mr. Friedman noted that these observations were consistent with our understanding of the data we have seen.

PURCHI-000675080 at 2.

⁸⁰ Dasgupta, et al. (2006). Association between non-medical and prescriptive usage of opioids. *Drug & Alcohol Dependence* 82:135-42. Indeed, as the CDC has stated in describing the opioid epidemic, "[f]rom 1999-2017, almost 400,000 people died from an overdose involving any opioid, including prescription and illicit opioids ... The first wave began with increased prescribing of opioids in the 1990s, with overdose deaths involving prescription opioids (natural and semi-synthetic opioids and methadone) increasing since at least 1999." *See* <https://www.cdc.gov/drugoverdose/epidemic/index.html>

⁸¹ The misleading promotional materials and statements discussed below are examples and do not represent an exhaustive list of such materials and statements.

⁸² For example, in a video produced by Purdue and titled "I Got My Life Back" that was duplicated in excess of 15,000 times, the physician/narrator Dr. Spanos stated the following:

Now, in fact, the rate of addiction amongst pain patients who are treated by doctors is much less than one percent. They don't wear out, they go on working, they do not have serious medical side effects. And so, these drugs, which I repeat, are our best, strongest pain medications, should be used much more than they are for patients in pain.

P450_00000213 at 10.

B. Purdue's Marketing Strategy for OxyContin

85. As explained in an internal memo written more than five years before OxyContin was approved, a key rationale of Purdue for developing OxyContin was to replace MS Contin, a controlled-release morphine product marketed by Purdue that was facing generic competition. In this memo, dated July 16, 1990, Dr. Robert Kaiko, Purdue's then-Vice President for Clinical Research and inventor of OxyContin, wrote "MS Contin may eventually face such serious generic competition that other controlled-release opioids must be considered." Dr. Kaiko recommended developing a controlled release oxycodone product, which later became known as OxyContin, because "[w]hile we have reason to believe that other pharmaceutical firms are formulating controlled-release morphine and controlled-release hydromorphone, there is no evidence to date that this is being done with oxycodone. A controlled-release oxycodone is, thus, less likely to initially have generic competition."⁸³

86. Minutes from Purdue's OxyContin Project Team meeting on June 8, 1994 noted that "OxyContin tablets will be targeted at the cancer pain market. Since it is possible that multiple generic products may soon be in competition with MS Contin Tablets, we will target

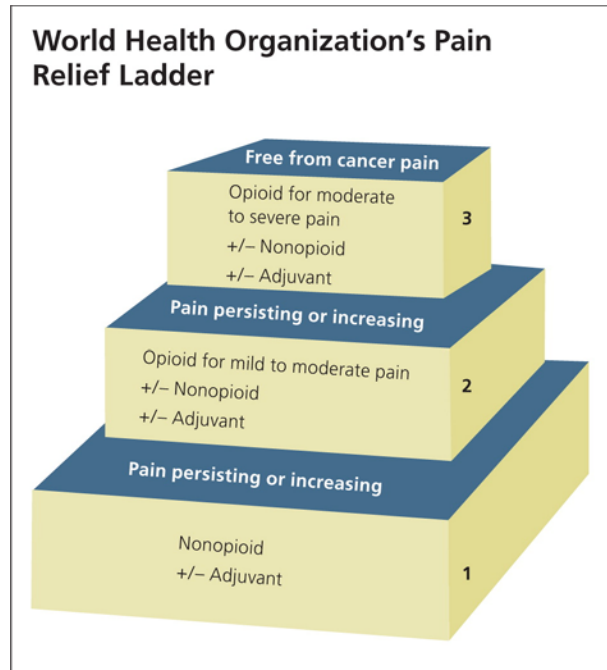
⁸³ PKY183276631 at 1-2. Dr. Kaiko repeated this rationale for developing OxyContin in a June 24, 1992 meeting of Purdue's Analgesics Committee. PPLP004030121 at 7. Notably, in the 1990 memo, Dr. Kaiko also recognized the abuse potential of oxycodone, stating:

It is interesting to note, however, that in the State of Connecticut and perhaps other states, the substance abuse officials consider oxycodone combinations among the most abused of Schedule II narcotic analgesic drugs. Dr. William T. Beaver of Georgetown University, in reviewing the clinical pharmacology of combination analgesics, has considered oxycodone a "sleeping giant" in that among all of the opioid analgesics utilized in fixed combinations, oxycodone is the only one with an analgesic potential comparable to that of morphine.

PKY183276631.

patients who are currently receiving MS Contin as well as those patients thought to eventually use MS Contin Tablets.”⁸⁴

87. According to Purdue’s research, most doctors and nurses reserved MS Contin for use in the final step of the World Health Organization’s three step ladder for cancer pain treatment.⁸⁵



88. This analgesic ladder was created by WHO to promote the sequential use of drugs to achieve cancer pain relief, in the following order:

Step 1: Use NSAIDs to treat mild pain

Step 2: Use weaker opioids to treat mild to moderate pain, i.e., oxycodone and hydrocodone combinations.

Step 3: Use strong opioids to treat moderate to severe pain. i.e., morphine.⁸⁶

⁸⁴ PPLP004030223 at 2; *see also* PURCHI-003286781 at 11 (“MS CONTIN will face competition from AB rated generic competitors. As a result, one of the major strategies in launching OxyContin will be to replace all prescriptions for MS CONTIN.”).

⁸⁵ PURCHI-003286781 at 12.

89. With MS Contin used primarily for the Step 3 treatment of moderate to severe cancer pain, Purdue, according to its OxyContin Launch Plan, positioned OxyContin to replace MS Contin and expand into Step 2 of the WHO analgesic ladder:

Opioid choices in treating moderate to moderately severe pain in Step 2 have been limited by oxycodone, hydrocodone, and codeine combination products. Their short-acting duration of action provides peaks and valleys in pain control. The combination of the opioid with APAP or ASA limits the maximum dosage because of potential liver toxicity. The APAP or ASA component also has the potential to mask a fever in the cancer patient. **All these problems associated with the choice of opioid analgesics in Step 2 present an opportunity for the introduction of a single-entity, long-acting oxycodone product.**⁸⁷

90. According to this launch plan, “Fixed combination opioids (oxycodone, hydrocodone, and codeine combined with APAP or ASA) have been the drugs of choice for treating moderate to moderately severe pain cancer pain (WHO step 2). ... These products are considered primary competition for OxyContin.”⁸⁸

91. In addition to expanding into the Step 2 pain market for cancer pain, Purdue described in its OxyContin Launch Plan the plan to expand OxyContin into the non-malignant pain market, stating:

⁸⁶ Achieving Balance in National Opioids Control Policy, Guidelines for Assessment, World Health Organization, 2000 at 37.

The first step is a non-opioid medication (such as aspirin, paracetamol, or ibuprofen). If this does not relieve the pain, an opioid for mild to moderate pain (such as codeine) should be added. When an opioid for mild to moderate pain in combination with a non-opioid medication does not provide effective analgesia, then an opioid for moderate to severe pain (such as morphine or one in the therapeutic group of morphine) should be substituted. Adjuvant drugs should be given at any point during drug treatment to relieve adverse effects of analgesics, to enhance pain relief, and to treat concomitant psychological disturbances such as insomnia, anxiety, and depression.

Id.

⁸⁷ PURCHI-003284938 at 2 (emphasis added).

⁸⁸ *See id.* at 3.

As soon as enough appropriate clinical studies are available for promotional claims, OxyContin will be launched into the chronic non-malignant pain market. The most common diagnoses for non-malignant pain are musculoskeletal pain, injury and trauma pain. The major competitors for these diagnoses will be oxycodone and hydrocodone combination products. OxyContin will be positioned as providing the equivalent efficacy and safety of oxycodone combinations, with the benefit of a q 12h dosing schedule.⁸⁹

92. This was not Purdue's first discussion about expanding OxyContin into the non-malignant pain market. In a June 24, 1992 meeting of Purdue's Analgesics Committee, Dr. Kaiko presented options for positioning OxyContin (then referred to as Oxycodone Acrocontin) in the United States market. The first option "envisaged using Oxycodone ACROCONTIN Tablets over the entire spectrum of pain in patients whose treatment had been initiated with this product."⁹⁰

93. According to Purdue's OxyContin launch plan, expanding into the Step 2 malignant pain market and the non-malignant pain market represented a potential Class II opioid market of \$462 million and a potential Class III opioid market of \$421 million.⁹¹

94. Similarly, Purdue's then-Group Vice President of Marketing & Sales, Michael Friedman wrote a "VERY CONFIDENTIAL" memo on December 29, 1994—the day after Purdue submitted the New Drug Application for OxyContin⁹²—discussing how OxyContin could be expanded into the non-malignant pain market:

⁸⁹ See *id.* at 16; see also PPLP004030223 at 2 (identifying future non-malignant pain markets for OxyContin as including "musculoskeletal pain (back pain, osteoarthritic pain), injury trauma, and post-operative").

⁹⁰ PPLP004030121 at 7; see also PPLP004026832 at 5.

⁹¹ PURCHI-003284938 at 7-8.

⁹² PURCHI-000572404. Notably, in describing the development of OxyContin in the NDA, Purdue focused on the cancer pain market and did not address use of OxyContin for non-malignant pain:

Oxycodone hydrochloride is an opioid analgesic which has been in human use since 1915. In the United States oxycodone-containing products have been marketed for a number of years. While oxycodone/acetaminophen and oxycodone/aspirin oral dosage forms represent the bulk of

If we consider the [W.H.O.] analgesic ladder as a continuum along which we position each of the products that we propose for development, the following is how we would position our proposed development program:

1. MS Contin currently covers most of Step 3 and reaches into Step 2. Eighty percent of the use of MS Contin is in cancer, however, over one-third of the prescription are written by FPs [Family Practitioners] / GPs [General Practitioners] & IMs [Internal Medicine]. We will continue aggressive promotion of MS Contin.
2. OxyContin will cover most of Step 3, all of Step 2 and could reach down into Step 1. We expect our initial promotion of OxyContin to be directed at current prescribers of single-agent opioids and oxycodone combinations; however we will not limit our promotion of OxyContin to cancer pain. We expect that over time the FPs/GPs & IMs that prescribe the drug for cancer pain will use the drug for other types of pain. We will direct this movement through the use of clinical studies, some of which will be available shortly after launch. We hope that the use of OxyContin will expand beyond the FP/GP & IM group into the other physician groups that use oxycodone combination and Class III drugs for post-operative, musculoskeletal, injury trauma, CNS, and other pain. OxyContin will be promoted at launch with most of our sales and marketing resources.⁹³

95. Likewise, in meeting minutes from the April 4, 1995 OxyContin Launch Team Meeting, Purdue's Head of Marketing, Mike Innaurato, stated that "OxyContin's primary market positioning will be for cancer pain and the secondary market will be for non-malignant pain

oxycodone prescriptions, **oxycodone immediate-release tablets (5 mg) and oral solution (5 mg/mL and 20 mg/mL) are available and have been used in the treatment of chronic cancer pain** (Glare and Walsh, 1993). The Purdue Frederick Company has experience in marketing analgesic products (Trilisate Tablets/Liquids, DHCplusTM Capsules and MS Contin Tablets). **Experience in the chronic cancer pain market with MS Contin led to the development of a second generation Contin product for patients who could not tolerate MS Contin or who preferred to remain on oxycodone as the dose requirement increased. The result was OxyContinTM Tablets** (oxycodone hydrochloride controlled-release tablets). This product employs a modification of the MS Contin controlled-release technology called ACROCONTINTM

Id. at 246 (emphasis added).

⁹³ PPLP004030154 at 6-7.

(musculoskeletal, injury and trauma).” He further “reinforced that we do not want to niche OxyContin just for cancer pain.”⁹⁴

C. Purdue Promoted OxyContin in a Manner that Understated its Risks, Overstated its Benefits, and for Indications that Lacked Substantial Evidence to Support Safety and Efficacy.

96. According to a December 29, 1994 internal Purdue memo, moving OxyContin into the non-cancer pain market would open OxyContin up to millions of new prescribing opportunities:

It is not unreasonable to assume that the first target for OxyContin will be the 1.5 Million prescriptions currently generated for single-agent opioids, followed by the 900,000 prescriptions currently written for cancer patients using oxycodone combinations. This approach will lead to greater use by physicians for the patients receiving the other 10+ Million prescriptions for oxycodone combinations, for other indications. If price does not become a significant barrier, market expansion into chronic non-malignant pain could lead to the use of OxyContin in the 68.7 million prescription Class III market.⁹⁵

97. To do so, according this same internal Purdue memo, entailed making physicians comfortable with the use of OxyContin in place of oxycodone combinations, such as Percocet, and building credibility with two groups of doctors: (1) oncologists and (2) family practitioners, general practitioners, and internal medicine physicians:

If physicians perceive OxyContin as controlled-release Percocet it is likely that they will start to use it in place of oxycodone combinations. As physicians become more comfortable with use in the oxycodone combination market it is possible that they will also start to use OxyContin in place of Class III hydrocodone or codeine combination drugs....

The port of entry to the oncology market will be oncologists and those FPs/GPs/IMs that currently treat cancer patients. By targeting both of these groups we will establish credibility in the Oncology market. The use of

⁹⁴ PPLP004030253 at 1 (emphasis in original).

⁹⁵ PPLP004030154 at 4-5.

OxyContin in Cancer pain patients, initiated by their Oncologists and then referred back to FPs/GPs/IMs, will result in a comfort level that will enable expansion of use in chronic non-malignant pain patients also seen by the family practice specialists. As we build clinical literature and the FDA becomes more comfortable with our promotion we will be in a position to move our promotion more aggressively into the indications currently reserved for oxycodone combinations and Class III combinations, specifically post-operative pain, musculoskeletal pain, injury/trauma, and CNS pain.⁹⁶

98. A year later, after receiving initial FDA approval for OxyContin, Purdue instructed its sales representatives to aggressively promote OxyContin, noting in a December 17, 1995 OxyContin memorandum that “OxyContin will be the most promoted product in Purdue history.”⁹⁷

99. In my opinion, this aggressive promotion targeted the groups of doctors identified in Purdue’s internal memo, and as explained below, utilized promotional tactics that misbranded OxyContin as a drug that is safer and more effective than it actually is without substantial evidence.

1. Purdue’s Promotion of OxyContin and Opioids in General Minimized the Risks of Abuse, Addiction, Tolerance, and the Effects of Withdrawal.

(a) Purdue’s Marketing Misleadingly Minimized the Similarities Between OxyContin and Morphine.

100. OxyContin is and always has been pharmacologically similar to morphine, including with respect to abuse liability.

100.1. In the NDA for OxyContin, Purdue stated “Oxycodone is an opioid with pharmacologic actions similar to morphine.”

⁹⁶ *Id.*; see also PKY180544129 at 428 (Purdue’s market research anticipated that “a comfort level will be established among FPs [Family Physicians] which could expand to include OxyContin for selected non-cancer pain.”).

⁹⁷ PKY180242947 at 2.

100.2. FDA's Pharmacology Review of the OxyContin NDA concluded that OxyContin is "pharmacologically similar to morphine."⁹⁸

100.3. FDA's Medical Officer Review found that the "distribution of adverse events by body system for CR Oxycodone [OxyContin] is similar to that reported for morphine sulfate."⁹⁹

100.4. The initial OxyContin label stated "OxyContin is a mu-agonist opioid with abuse liability similar to morphine."¹⁰⁰

100.5. The current label for OxyContin contains similar language.¹⁰¹

101. Purdue's pre- and post-approval market research identified a negative "stigma" associated with morphine as to addiction.

101.1. At an OxyContin Investigator's Meeting in June 1995, results from an opioid stigma survey were reported, noting that "among health care providers there is a perception that patients feel a 'stigma' associated with opioid analgesic therapy.

Morphine and hydromorphone are most associated with this stigma. One of the patients' biggest fears appears to be the possibility of addiction..."¹⁰²

⁹⁸ PURCHI-000667209 at 140.

⁹⁹ PURCHI-000667209 at 34.

¹⁰⁰ SHC-000006346 at 6. Notably, FDA approved OxyContin for an indication similar to that of Purdue's extended-release morphine product, MS CONTIN. *See id.* at 3 ("OxyContin is intended for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days.") *compare* MS Contin Label, Jan. 28, 1994, PDD1715073161 at 1 ("[I]ndicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesics over periods of more than a few days."); *see also* MS Contin 1996 PDR at 2.

¹⁰¹ *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022272s040s041lbl.pdf (last visited March 15, 2019).

¹⁰² PKY181823986 at 17; PPLP004030121 at 2; PPLP004030223 at 2; PPLP004030214 at 9; SHC-000004120 at 62.

101.2. This “stigma” was confirmed in focus groups paid for by Purdue and comprised of doctors and nurses in multiple fields, which reported that “there is no question that morphine has a negative stigma with patients relative to both addiction and the terminal nature of their illness.”¹⁰³

101.3. The 1996 OxyContin Formulary Kit copyrighted by Purdue repeated this conclusion, stating “[m]isapprehension concerning the risk of addiction and poor understanding of the concepts of tolerance and physical dependence are part of the problem... Morphine bears a disproportionate share of the stigma associated with opioids, which is intensified by the drug's historic association with terminal disease and helplessness, and with the opium ‘taboo.’”¹⁰⁴

101.4. In a May 28, 1997 email from Purdue’s Michael Friedman to Dr. Richard Sackler, Friedman described the “personality” of OxyContin as being weaker than morphine:

[W]e are well aware of the view, held by many physicians, that oxycodone is weaker than morphine. We all know that this is the result of their association of oxycodone with less serious pain syndromes. This association arises from their extensive experience with and use of oxycodone combinations to treat pain arising from a diverse set of causes, some serious, but most ‘less serious.’ This ‘personality’ of oxycodone is an integral part of the ‘personality’ of OxyContin.”¹⁰⁵

102. The marketing proposals received by Purdue to develop the OxyContin brand recommended utilizing the morphine stigma to gain a competitive advantage for OxyContin.

¹⁰³ PKY181004545 at p. 23; *see also* SHC-000001965 at 2; SHC-000026456 at 46; PKY181004480 at 32; PKY181386644 at 34.

¹⁰⁴ ABT-MDL-KY-0002826 at 11.

¹⁰⁵ PPLP004030150 at 1.

102.1. One advertising agency submitted a proposed brand strategy on April 25, 1994 that highlighted the stigma attached to morphine, asking “how can we capitalize on the perception among patients and physicians that OxyContin does not carry the stigma of morphine through indirect means.” The plan emphasized that one of the “emotional advantages” of OxyContin was that there was “no morphine stigma relating to perception about addiction, tolerance, excessive power, end stage treatment.”¹⁰⁶

102.2. Other advertising agencies similarly proposed brand plans that highlighted the need to differentiate OxyContin from morphine, with one advertising agency recommending that Purdue “separate OxyContin from the ‘addiction’ stigma of morphine-containing products”¹⁰⁷ and another agency noting that the “fear of morphine addiction on the part of patients is a real barrier to treatment of pain. Because of the social issues, people would prefer to take 40 mg of oxycodone rather than 5 mg of morphine.”¹⁰⁸

102.3. In May of 1994, Purdue hired the advertising agency Lavey/Wolff Swift, Inc.,¹⁰⁹ whose proposed brand strategy highlighted that “oxycodone does not carry the stigma or many of the side effects of morphine or other third-step opioids....”¹¹⁰

103. Purdue’s marketing of OxyContin utilized the “stigma” associated with morphine to differentiate OxyContin from morphine, despite their well-known similarities.

¹⁰⁶ PKY180286806 at 11, 13, 38.

¹⁰⁷ PKY180286896 at 39-40.

¹⁰⁸ PKY180287212 at 3.

¹⁰⁹ PKY180250286 at 5.

¹¹⁰ PKY180286723 at 58.

103.1. In the same May 28, 1997 email described above, Friedman explained to Dr. Sackler how Purdue used this “personality” of OxyContin being weaker than morphine in its marketing, writing:

When we launched OxyContin, we intentionally avoided a promotional theme that would link OxyContin to cancer pain. We specifically linked OxyContin to the oxycodone combinations with our “old way, new way” campaign. We made sure that our initial detail piece provided reps with the opportunity to sell the product for a number of different pain states.¹¹¹

103.2. Friedman continued, “it would be extremely dangerous, at this stage in the life of this product, to tamper with this ‘personality,’ to make physicians think the drug is stronger or equal to morphine.”¹¹²

103.3. The following month, on June 22, 1997, Purdue’s Marketing Group Manager for OxyContin, Michael Cullen, reminded the OxyContin product team of the “perception” of OxyContin as weaker than MS Contin and stressed importance of not changing this “perception” in promotional materials:

Since oxycodone is perceived as being a “weaker” opioid than morphine, it has resulted in OxyContin being used much earlier for non-cancer pain. Physicians are positioning this product where Percocet, hydrocodone, and Tylenol with Codeine have been traditionally used.

Since the non-cancer pain market is much greater than the cancer pain market, it is important that we allow this product to be positioned where it currently is in the physician's mind. If we stress the “Power of OxyContin” versus morphine, it may help us in the smaller cancer pain market, but hurt us in the larger potential non-cancer pain market. Some physicians may start positioning this product where morphine is used, and wait until pain is severe before using it.

...

¹¹¹ PPLP004030150 at 1.

¹¹² *Id.*

It is important that we not change the position perception of physicians towards oxycodone when developing promotional pieces, symposia, review articles, etc.¹¹³

103.4. In a June 16, 1997 marketing and sales update, Michael Cullen reminded the OxyContin team that “we can show that we are as ‘effective’ as morphine, but do not want to say OxyContin is as ‘powerful’ as morphine. Words such as ‘powerful’ may make some people think the drug is dangerous and should be reserved for the more severe pain.”¹¹⁴

104. According to Purdue’s marketing team, by differentiating OxyContin from morphine, Purdue was able to expand OxyContin beyond the cancer pain market.

104.1. As noted by Michael Friedman in his email to Dr. Sackler on April 22, 1997, “despite our initial uncertainty, we have been successful beyond our expectations in the non-malignant pain market. Doctors use the drug in non-malignant pain because it is effective and the ‘personality’ of OxyContin is less threatening to them, and their patients, than that of the morphine alternatives.”¹¹⁵

104.2. In another email to Dr. Richard Sackler, Friedman explained that Purdue used this “personality” of OxyContin being weaker than morphine to differentiate OxyContin from MS CONTIN with great success:

Oxycodone has a ‘personality that is influenced by many years of oxycodone use in Percocet. We have built a large part of our platform on this personality and used it to differentiate OxyContin from MS Contin and This differentiation has lead [sic] to much non-malignant business. Marketing is not only about who you are. It is also about what

¹¹³ PPLP004032323 at 4.

¹¹⁴ PPLP004030366 at 1. To that effect, in a sales PowerPoint titled “OxyContin Competitive Market,” Purdue described morphine as “the most potent analgesic” despite OxyContin being more potent than morphine. *See* SHC-000000508 at 37

¹¹⁵ PPLP004030150 at 1.

you are not. We have a success beyond our expectations that is, in part, due to the unique personality of OxyContin.”¹¹⁶

104.3. Years later, on January 25, 2001, Friedman confirmed the success of Purdue’s strategy to distinguish OxyContin from morphine in an email to Mark Alfonso, Purdue’s Executive Director of Marketing, stating that “we were able to convince doctors to use OxyContin tablets because of its position in the doctors mind that is [sic] very different from morphine.”¹¹⁷

105. In my opinion, Purdue’s marketing minimized the similarities between OxyContin and morphine.

(b) Purdue Falsely Marketed OxyContin as Having a Lower Potential for Abuse as Compared to Other Opioid Products

106. Purdue’s early market research also identified the “**biggest negative** of the product [OxyContin] **was the abuse potential**...this was exacerbated by the fact that some felt that Q12h dosing and the lack of APAP or ASA, might make the product more susceptible to addiction.”¹¹⁸

107. To address the reluctance of physicians to prescribe OxyContin for non-cancer pain, market researchers recommended that “Purdue Frederick implement clinicals with OxyContin among non-cancer pain patients to determine if there might be any reductions in side effects that one might get when compared with the combination opioids,” noting that “[i]f the

¹¹⁶ PPLP004030162 at 1.

¹¹⁷ PPLP004030463 at 1.

¹¹⁸ PPLP004031668 at 39. In a December 3, 1996 report titled “OxyContin Research: Self-Administered Questionnaire Among Rheumatologists Prescribers and Non-Prescribers of OxyContin,” which was commissioned by Purdue, it was shown that the most frequently mentioned reason for why a physician would not prescribe OxyContin was “abuse potential (22%).” SHC -000007578 at 3.

product was proven to have a lower abuse potential than IR [immediate release] oxycodone, it would improve the likelihood of usage for non-cancer pain.”¹¹⁹

108. Purdue never conducted a clinical trial specifically evaluating, much less providing substantial evidence, that OxyContin had a lower abuse potential as compared to immediate release oxycodone or any other opioid product.¹²⁰

108.1. In 1993, Purdue conducted a “spoon and shoot” study to determine what constituents could be extracted by grinding OxyContin into a solvent traditionally used by addicts. Purdue and FDA acknowledged the ease in which Oxycodone HCL could be easily extracted in water, “a fact which abusers would most likely learn very quickly.”¹²¹

108.2. Purdue conducted a 4-year registry study, OC97-0302, that evaluated, among other things, instances of drug abuse among patients taking OxyContin.¹²² “Of the 233 subjects who enrolled in OC97-0302, 13 subjects were indicated by the investigators as having signs of ‘drug seeking behavior’ on the case report form.”¹²³ A review by the External Advisory Board (EAB) overseeing the RADARS System (Researched Abuse, Diversion, and Addiction-Related Surveillance System) reduced the number of subjects to 6.¹²⁴ Based on this reduced number, Purdue concluded that “the frequency of ‘drug seeking behavior’ cases that were considered positive or possible for drug abuse or dependence in this study” was no different than the prevalence of drug abuse in the

¹¹⁹ PPLP004031668 at 58. The recommendation by market researchers aligned with the recommendation by FDA that Purdue conduct a long-term OxyContin study of “highly selected” patients with osteoarthritis to examine, among other things, the abuse liability of OxyContin. SHC-000002018 at 1.

¹²⁰ PDD1701345999 at 1-2.

¹²¹ SHC-000007033 at 9.

¹²² See SHC-000007763 at 26

¹²³ See PDD8013445789 at 3223-3224.

¹²⁴ *Id.*

general population based on reports to the National Household Survey on Drug Abuse (NHSDA).¹²⁵

109. In addition, in 1992, 1994, and 1997, Purdue acknowledged that the question of whether OxyContin's extended release design reduced the abuse liability of the drug had not been studied.

109.1. In draft OxyContin labels from 1992 and 1994, Purdue wrote that "parenteral oxycodone has comparable abuse liability to parenteral morphine" and "whether or not the controlled-release dosage form" of OxyContin "would have the same effect is unstudied at present."¹²⁶

109.2. On February 27, 1997, after learning that Purdue was considering selling OxyContin in Germany as an uncontrolled "non-narcotic," which would eliminate the requirement to track instances of abuse, Purdue's then-Vice President of Clinical Research and the inventor of OxyContin, Dr. Robert Kaiko, responded:

b) I don't believe we have a sufficiently strong case to argue that OxyContin has minimal/or no abuse liability:

- in the U.S. oxycodone containing products were once less controlled than now; abuse resulted in greater controls;
- oxycodone containing products are still among the most abused opioids in the U.S.; this information is available to BfArM;
- the local tissue necrosis that can result from injection of OxyContin "fixed" for such abuse is not likely to be a deterrent to abuse; let us not forget that in New Zealand, MST is the most common sources of parenterally abused morphine/heroin;
- **our dossier acknowledges a small handful of patients in our research program who were suspect in terms of their drug accountability;**

¹²⁵ *Id.*

¹²⁶ PDD150109445 at 12; PDD1501101593 at 18. This language was included in the draft package insert submitted by Purdue to FDA as part of the original NDA for OxyContin. See PURCHI-000621046. For reasons unknown at the time of this report, the language appears to have been deleted by FDA during the course labeling negotiations. See PPLPC024000000134; see also PPLP004030136 ("[W]e do not have any abuse liability studies.").

- we do not have a postmarketing abuse monitoring system and data base from which we could conclude that diversion/abuse is not occurring.

c) **If Oxycontin is uncontrolled in Germany, it is highly likely that it will eventually be abused there and then controlled.** This may be more damaging to OxyContin internationally than any temporarily higher sales that would be gleaned from an uncontrolled status; let us not forget the experience with buprenorphine, which was initially uncontrolled: reports of abuse in Germany, in part, eventually led to lots of bad press and controlled status; worldwide sales suffered - even where buprenorphine had been already controlled.¹²⁷

110. Moreover, FDA specifically instructed Purdue not to make claims comparing the OxyContin to other opioid products and rejected any claim of superiority over other opioid products with respect to efficacy and safety. Specifically:

110.1. In the Integrated Summary of Safety (ISS) completed by Dr. Curtis Wright, IV on May 19, 1995 as part of the FDA Medical Officer Review, Dr. Wright stated that “[t]he best conclusion is that the efficacy of [OxyContin] is equivalent to the [immediate-release oxycodone], with an adverse event profile that is as good as the [immediate-release oxycodone]. I would not allow a ‘better’ claim.”¹²⁸

110.2. Dr. Wright also noted in the ISS that “[t]he adverse experience profile of [OxyContin] is qualitatively similar to that of the parent drug, oxycodone;”¹²⁹

110.3. In the FDA Medical Office Review’s Integrated Safety of Efficacy (ISE) completed by Dr. Wright on June 19, 1995, he stated “[t]here is some evidence, both pharmacokinetic and clinical, that reduced acute opioid adverse effects may be expected

¹²⁷ PDD1701345999 at 1-2 (emphasis added).

¹²⁸ PURCHI-000667209 at 37 (original emphasis).

¹²⁹ PURCHI-000667209 at 39.

in some patients, but there is not enough evidence to support an [adverse event] superiority claim [for OxyContin] against other marketed products;”¹³⁰ and

110.4. In the ISE, Dr. Wright also noted that “[c]are should be taken to limit competitive promotion. [OxyContin] has been shown to be as good as current therapy, but has not been shown to have a significant advantage beyond reduction in frequency of dosing.”¹³¹

111. Nonetheless, Purdue’s sales representatives were trained to make misleading statements unsupported by substantial evidence that OxyContin had lower abuse potential as compared to other opioid products, utilizing this statement that was added to the initial label approved for OxyContin: “Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.”¹³²

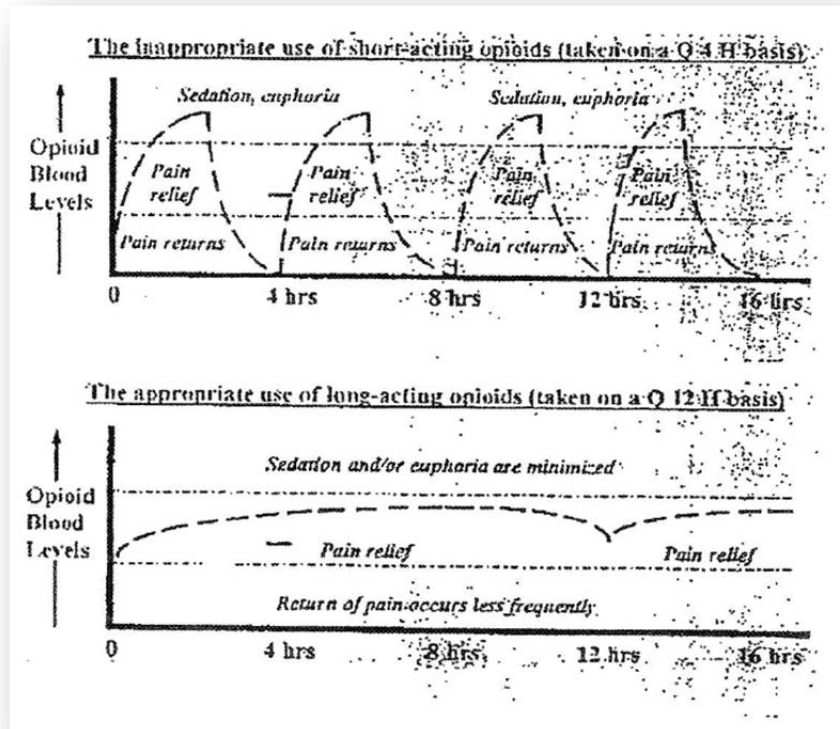
111.1. For example, Purdue held a training session in or about December 1998 for all of its district sales managers where it “falsely stated that OxyContin has significantly fewer ‘peak and trough’ blood level effects than immediate-release opioids resulting in less-euphoria and less potential for abuse than short-acting opioids” and used

¹³⁰ PURCHI-000667209 at 40.

¹³¹ PURCHI--000667209 at 53.

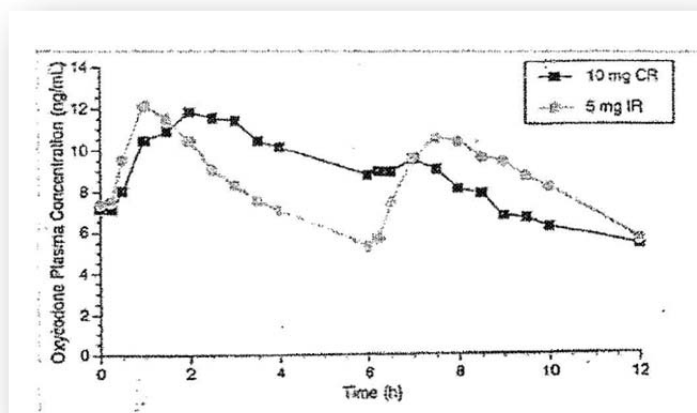
¹³² SHC-000006346 at 6. In response to media reports, Robert Reder, M.D., Purdue’s Vice President, Medical Director has stated that he believes the delayed absorption language was added by FDA. *See* Purdue Pharma Stmt on The Uncertain Hour’s OxyContin episode, December 13, 2017, *available at* <https://www.marketplace.org/2017/12/13/health-care/purdue-statement> (last visited March 15, 2019). This is contradicted by August 2, 1995 handwritten edits to the OxyContin label, which added the delayed absorption language, and were made *after* FDA reviewers submitted their labeling edits to Purdue. *See* SHC-000004520 at 19; *see also* PPLPC02400000133 (circulating FDA edits to OxyContin PI); PPLPC02400000134 (attachment to email). Further, a review of Purdue’s communications log with FDA does not reveal any contact with FDA on or near August 2, 1995 such that FDA directed Dr. Reder to add this language. *See* PPLPC001000135671. In 2001, FDA directed Purdue to remove this language from the label. *See* SHC-000008186. In the deposition of Dr. Curtis Wright, IV, he testified that “I don’t know” who proposed the language “delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.” Wright Dep. Tr. 156:16-25, 158:05-14, Dec. 19, 2018. However, Dr. Wright confirmed that the handwritten edits mentioned above were not his. *Id.* at 158:15-159:02.

the following graphical demonstration that was not based on clinical trial data and contravened a prior instruction by FDA to refer to actual data in these demonstrations:



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¹³³ PDD1712900035 at 8-9; PURCHI-000622957 at 11-12. Below is a graph that accurately portrays the peaks and troughs by blood plasma levels for both OxyContin and immediate release oxycodone, which DDMAC instructed Purdue to use in lieu of the above promotional graphs. PDD1712900035 at 6-7.



111.2. In addition, during training at Purdue's headquarters in or around 1999, "some of PURDUE's new sales representatives were permitted ... to draw their own blood level graphs to falsely represent that OxyContin, unlike immediate-release or short-acting opioids, did not swing up and down between euphoria and pain, and resulted in less abuse potential."

111.3. In handwritten notes from a Purdue sales training that outlined responses to statements from doctors, a sales representative wrote "↑ abuse potential" in response to the statement "I prefer CIII's because I can call them in."¹³⁴

111.4. In undated sales force training materials, Purdue outlined questions to be asked of physicians misleadingly suggesting that OxyContin has low abuse potential:

9. (Using the ladder) "How would you feel about using a drug with:
a, the same indication as Vicodin and Ultram on the low end
b. with q12h dosing and **low abuse potential**
C. as your first pain medication after NSAIDs?

10. (Using the ladder): "How comfortable would you be initiating analgesic therapy after NSAIDS with a dosing regimen more mild than Tylenol #3 dosed q 4h, and **with a low abuse potential?**"

11. (Using the PDB page 24 Figure 7) "Doctor, that's excellent that you are concerned about abuse, that's exactly why the experts are using OxyContin take a look at this graph...**which drug do you think is most likely to lead to abuse potential, the one that dumps all the drug within the first hour causing this spike, or the one the enter the blood stream slowly and smoothly?**"

12. (Using the PDB page 7, last sentence in first paragraph) "Doctor, how do you feel about this statement...do your patients really set their alarm docks at midnight and 4 am? How would you feel if you could prevent this and give the patient pain prevention with **minimum abuse potential?**"

13. "Doctor, Mr. Wil Corbitt, diversion program coordinator for the DEA in the state of Florida, spoke to our group in November 1997. What do you

¹³⁴ SHC-000008102 at 2.

think he said is the biggest street abused drug in Florida? (answer: hydrocodone)...How would you feel about using a pain management tool that, according to the FDA, may have a **reduced abuse potential**?

...

15. "I am worried about my patient becoming dependent on OxyContin (or drugs like it)?" Ask the doctor, "Now do you mean dependent?" Introduce new visual aid and proper definitions Doctor, that's exactly why you should use OxyContin. Show APS page 26 ...risk of iatrogenic addiction is rare show blood levels on page 7 of PDB —Doctor, **which blood level do you think would be more likely to lead to abuse??**

...

26. If there were a pain medication that could provide 96.5% success right after NSAIDs, **with a reduced abuse liability**, how would you feel about using this product? (show package insert or product data brochure validating this success rate)

...

30. Doctor, how would you feel if one pain medication could control moderate pain right after NSAIDs as well as severe pain with a 96.5% success rate and **a reduced abuse potential**?¹³⁵

112. Aligning with the sales training provided by Purdue, Purdue's sales force falsely told health care providers in all fifty states¹³⁶ that the language in the OxyContin label regarding the possibility of reduced abuse potential "meant that OxyContin did not cause a 'buzz' or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used to 'weed out' addicts and drug seekers."¹³⁷ For example, Purdue's internal call notes for OxyContin include the following misleading statements by Purdue's sales force:

112.1. May 22, 1996 (Kentucky) - "RETOLD ME THAT CLASS MADE A BIG DIFFERENCE AND **HE FELT THAT HYDORCODONE IS LESS ABUSED, AFTER HEARING THAT IT IS MUCH MORE ABUSED** AND TALKING ABOUT THE ABUSE ISSUES, HE TOLD ME THAT HE WOULD USE IT AND WOULD USE

¹³⁵ SHC-000026573 at 1-4.

¹³⁶ Shapiro Dep. Tr. 235:15-236:01, April 15, 2015, PPLP004030873.

¹³⁷ *Id.* at 210:21-211:12.

IT PREOP. I POINTED OUT THE PI, BUT HE FEELS THAT HE WOULD USE IT PREOP AS WELL AS POSTOP.”¹³⁸

112.2. November 7, 1997 (Ohio) - “ALWAYS RELUCTANT TO USE NARCS BUT TOLD IF GOING TO PUT PT ON VIC/LORT OR TYL 3, WHY NOT USE THE 12 HR DOSED, WITHOUT TYLENOL AND LESS ABUSE POTENTIAL.”¹³⁹

112.3. January 22, 1998 (Ohio) - “THOUGHT OXY WAS JUST FOR CA AND CHRONIC PAIN. TOLD LIKE Q12 HR VIC OR LORTAB/USED FOR ANY TYPE OF PAIN LASTING MORE THAN 4 DAYS.LESS ABUSE POTENTIAL”¹⁴⁰

112.4. May 21, 1998 (Ohio) - “DOES TREAT PAIN/INTERESTED IN-OXY ASKED FOR ANY PTS ON VIC/ORE THAN SEVERAL DAYS. TOLD LESS ABUSE/NO TYLENOL...”¹⁴¹

112.5. August 6, 1998 (Ohio) - “OXY FOR ALL VIC PTS/LESS ABUSE POTENTIAL AND PTS CAN SLEEP THROUGH PM.”¹⁴²

112.6. September 18, 1998 (Ohio) - DR. HAS A TON OF VICO PTS. A LOT OF LOW BACK PAIN. LEARY OF CLASS II'S. USED PI TO SELL LOW ABUSE, Q12H, AND QOFL. DR. AGREED TO USE FOR ALL OF HIS LOW BACK INSTEAD OF VICO. KEEP ON THIS GUY, THIS IS EASY MONEY.¹⁴³

¹³⁸ PPLP004032436 (emphasis added). Call notes are reproduced with minimal, if any, changes to formatting, grammar, spelling, etc., including use of all capital letters. Additional call notes can be found in Schedule 11.

¹³⁹ PKY182139780 (emphasis added).

¹⁴⁰ PKY182139597 (emphasis added).

¹⁴¹ PPLPMDL0030008507 (emphasis added).

¹⁴² PPLPMDL0030008507 (emphasis added).

¹⁴³ PPLPMDL0080000001 (emphasis added).

112.7. July 6, 1999 (Ohio) - “Hit Oxy, **does not like to prescribe narcotics because of abuse and addiction. Turned both objections into adv for Oxy.** Dr liked the fact of low abuse and drastically less tabs.”¹⁴⁴

112.8. July 15, 1999 (Ohio) - Dr. admitted that he has been seeing a ton of drug seekers lately. Has stopped giving oral opioids and will give only an injection. **Hit on low abuse and how pts. would call back screaming if they were given the Oxy in place of the Perco. Dr. agreed.**¹⁴⁵

112.9. September 20, 1999 (Ohio) - “**Dr. thinks that he is going to get busted since he is writting so much Oxy. Reminded him of less tabs and lower abuse.** Discussed using for post op pain esp those chronic painers and how to use as much Oxy to address pts. pain. Discussed tolerance.”¹⁴⁶

112.10. December 18, 2000 (Ohio) - Did get him to admit that **pts. in a LTC would be a good choice for O.C. b/c of low abuse potential** and I shared the Marcus reprint with him.¹⁴⁷

113. Purdue’s sales force likewise falsely told health care providers “that OxyContin has significantly fewer ‘peak and trough’ blood level effects than immediate-release opioids resulting in less-euphoria and less potential for abuse than short-acting opioids.”¹⁴⁸

¹⁴⁴ PPLPMDL0080000001 (emphasis added).

¹⁴⁵ PPLPMDL0080000001 (emphasis added).

¹⁴⁶ PPLPMDL0080000001 (emphasis added).

¹⁴⁷ PPLPMDL0080000001 (emphasis added).

¹⁴⁸ Attach. B to Plea Agreement of *U.S. v. The Purdue Frederick Co. Inc.*, Agreed Statement of Facts, PDD1712900035 at 6.

114. Purdue later stated that “from December 12, 1995 through June 30, 2001, Purdue marketed and promoted OxyContin as ... less subject to abuse and diversion ... than other pain medications.”¹⁴⁹

115. In my opinion, Purdue falsely marketed OxyContin as having a lower potential for abuse as compared to other opioid products.

(c) Purdue Lacked Substantial Evidence Regarding the Addictive Potential of OxyContin, Yet Misleadingly Claimed that OxyContin Was Less Addictive than Competitor Opioid Products.

116. Opioid products, including oxycodone, are addictive.

116.1. The medical literature has recognized the addictive potential of opioids.¹⁵⁰

116.2. The initial OxyContin label warned that OxyContin “may be habit forming.”¹⁵¹

116.3. Purdue acknowledged in 2001 the lack of substantial evidence regarding the rate of addiction, stating “there are no data to accurately characterize the extent of addiction” among patients taking opioids.¹⁵²

¹⁴⁹ *Id.* at 4, 5.

¹⁵⁰ *See, e.g.* Bloomquist. (1963) The Addiction Potential of Oxycodone (Percodan). Reports on Drugs. 99:2; Bouckoms et al. (1992) Chronic Nonmalignant Pain Treated with Long-Term Oral Narcotic Analgesic. Annals of Clinical Psychiatry. 4:3; Fishbain et al. (1992). Drug Abuse, Dependence, and Addiction in Chronic Pain Patients. Clinical J Pain. 8:77-85.

¹⁵¹ *See, e.g.*, SHC-000006346.

¹⁵² SHC-000020630 at 10. Notably, published historical clinical experiences with opioids indicated that iatrogenic addiction was not rare among patients using opioids for prolonged periods of time. *See* Portnow J. (1985). Medically Induced Drug Addiction. Intl J Addict 20:605-611 (“Medically induced drug addiction as a complication of medical treatment is being increasingly recognized as a widespread problem demanding new and innovative solutions.”); Musto D. (1985). Iatrogenic Addiction: the problem, its definition and history. Bull NY Acad Med 61:694-705; Walker L. (1978). Iatrogenic Addiction and Its Treatment. Intl J Addict 13:461-473.

117. From pre-approval market research conducted in 1994 and 1995, Purdue learned that “[t]he medical community is looking for a product that would be efficacious for severe pain, **particularly if it could avoid the . . . addictive potential of the opioids.**”¹⁵³

118. Despite the lack of substantial evidence regarding the addictive potential of opioids and FDA’s instruction not to make claims comparing OxyContin to other opioids,¹⁵⁴ Purdue trained its sales force to tell doctors that the addictive potential of opioids had been greatly exaggerated and that OxyContin was less addictive than competitor opioid products:

118.1. In its 1996 OxyContin launch plan, Purdue stated that “[p]hysicians, nurses and pharmacists are very often resistant to using scheduled drugs in the treatment of pain. This is due to a fear of patient drug addiction.” The plan noted that “[m]ost [physicians] are overly concerned with . . . addiction associated with opioid analgesics.”¹⁵⁵ Hence Purdue asserted in its 1996 Press Release for OxyContin that “[t]he fear of addiction is exaggerated.”¹⁵⁶

118.2. In Purdue’s 1998 marketing “War Book” for OxyContin, Purdue identified key “message points” designed to reinforce OxyContin’s advantage over competitors, one of which included OxyContin’s “low incidence of addiction or tolerance” as compared to competitors.¹⁵⁷

119. Other Purdue promotional materials downplayed the risk of addiction and were targeted at physicians.

¹⁵³ SHC-000026456 at 6 (emphasis added).

¹⁵⁴ See, e.g., PURCHI-000667209 at 36, 40, 53, 94.

¹⁵⁵ PURCHI-003284938 at 1.

¹⁵⁶ SHC-000024730 at 22.

¹⁵⁷ SHC -000004120 at 33.

119.1. On August 4, 1998, Purdue distributed to its entire sales force a sample letter to doctors on addiction. The letter downplayed the risk of addiction, stating “the risk of addiction to opioids in clinical care has been greatly exaggerated” and “[v]ery few patients taking opioids for pain fit this definition,” and instructing doctors to “look at the facts”—specifically, that:¹⁵⁸

[A] survey of more than 11,000 opioid-using patients, taken over several years, found that less than 1% (4 cases) of these patients had documented cases of addiction.

. . .

The risk of opioid abuse or addiction in patients without prior histories of abuse is extremely rare . . .

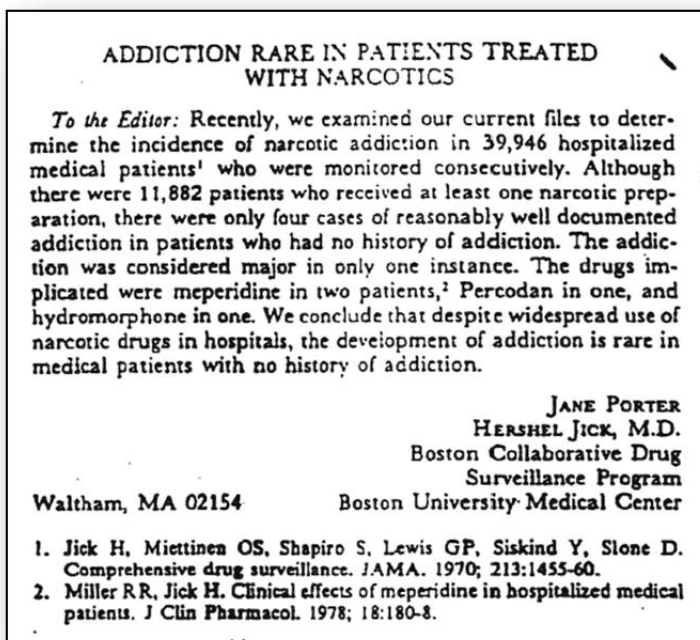
We're confident that effective pain management can be achieved in more patients if physicians like yourself look at the facts. By recognizing the fear of addiction, more and more patients can be helped with opioid therapy.¹⁵⁹

119.2. These “facts” originated from the following five sentence-long letter published by the New England Journal of Medicine in 1980 that provided no information on opioid dose, number of doses, duration of opioid treatment, extent of any long-term follow-up of patients, including whether opioid treatment was continued; or the criteria used to ascertain opioid addiction:¹⁶⁰

¹⁵⁸ PKY180117076 at 11.

¹⁵⁹ *Id.*

¹⁶⁰ Dr. Jick later admitted that he and Dr. Porter submitted the data in letter format to the New England Journal of Medicine because it was not robust enough to merit a study. *See* Barry Meir, *Pain Killer: An Empire of Deceit and the Origin of America's Opioid Epidemic* 33 (2d ed. 2018).



120. Aligning with the sales training provided by Purdue and Purdue's promotional materials, Purdue's sales force misleadingly told health care providers that opioids rarely led to addiction and that OxyContin was subject to less addiction than other opioid products, without substantial evidence:

120.1. November 19, 1997 (West Virginia) - "**CONCERNED ABOUT ADDICTION WITH OPIOIDS**. DIFFERENCE BETWEEN DEPENDENCE AND ADDICTION. **LESS THAN 1% OF PATIENTS BECOME ADDICTED**. CAN ABRUPTLY STOP LOW DOSES OF OXYCONTIN WITHOUT WITHDRAWAL SYMPTOMS"¹⁶¹

¹⁶¹ SHC-000008118 (emphasis added).

120.2. November 21, 1997 (New Jersey) - “HAS AN OPPORTUNITY TO RX PAIN MEDS IN ER AT ST FRANCIS IS CONCERNED WITH ADDICTION BUT AGREES THAT LONG ACTINGS ARE LESS LIKELY TO ADDICT”¹⁶²

120.3. April 23, 1998 (Ohio) - “RPH WAS CONCERNED WITH THE NUMBER OF PATIENTS THAT DR RICHMOND HAS PUT ON OXY, SD THEY ARE ALL PRETTY STRANGE DIS LESS ABUSE AND ADDICTION WITH OXY AND WHY MORE APPROPRIATE, DIVERSION RATE OF OXY VS OTHERS”¹⁶³

120.4. May 11, 1998 (Kentucky) - “USE OF FROM START TO WAS UNDER THE IMPRESSION THAT O WAS ONLY THERE TO REPLACE MSC. NOOOOOOO! SHOWED HIM PI INDICATION, PLUS THE NON-ADDICTIVE AND ACET PROBLEM. WHEN I LEFT HE SAID HE WAS SWITCHING THEM ALL OVER TO O FROM HYDROS WE'LL SEE.”¹⁶⁴

120.5. November 4, 1998 (Kentucky) - “BEFORE HAS A WORRY ABOUT THE DEA. TOLD HIM TO TELL THEM, IF ANYTHING EVER HAPPENED, THAT THE PURDUE REP TOLD THEM THAT IT WAS LESS ADDICTING”¹⁶⁵

120.6. March 9, 2001 (Kentucky) - “said speaker for purdue at recent FP mtg said oxy was not addicting.”¹⁶⁶

121. Purdue also created Partners Against Pain, a pain advocacy organization, to promote the claim that addiction to opioids is rare, despite lacking substantial evidence.

¹⁶² SHC-000008111 (emphasis added).

¹⁶³ PKY182142182 (emphasis added).

¹⁶⁴ PPLP004032436 at 80 (emphasis added).

¹⁶⁵ PPLP004032436 at 112 (emphasis added).

¹⁶⁶ PPLP004032436 at 401 (emphasis added).

121.1. For instance, a Partners Against Pain brochure issued in 2000 and titled “Counseling Your Patients and Their Families Regarding The Use of Opioids to Relieve Pain,” stated “a survey of more than 11,000 opioid-using patients, taken over several years, found only four cases of documented addiction” “among patients who regularly take opioids for pain, and have no history of substance abuse...which percentage represents the proportion who become addicted ... 1%.”¹⁶⁷ This brochure cited the Porter & Jick letter.

121.2. In a 2001 “Patient Bill of Rights,” Partners Against Pain stated that “[a]ddiction is very rare in patients without a history of drug/alcohol abuse when taking an opioid under a doctor’s care.”¹⁶⁸

122. Purdue also financially supported, and in some cases controlled, other pain advocacy organizations that put forth promotional materials and engaged in promotional activities that falsely claimed that the risk of opioid addiction had been exaggerated. The following is a brief summary of Purdue’s involvement in these advocacy organization and their false and misleading statements:

122.1. Purdue provided millions of dollars to pain advocacy organizations, including American Pain Foundation, Ameican Pain Society, American Academy of Pain Medicine, the Joint Commission, and the Federation of State Medical Boards.

122.2. These organizations published guidelines and other materials, provided continuing medical education, and otherwise purported to provide “education” to healthcare providers and patients regarding the safe use of opioids.

¹⁶⁷ SHC-000024493 at 11-13.

¹⁶⁸ SHC-000004944 at 5.

122.3. These promotional materials contained statements unsupported by substantial evidence and were therefore false and misleading as to the safe use of opioids, including that the rate of opioid addiction is exaggerated.¹⁶⁹

122.4. Further detail regarding Purdue's involvement in these pain advocacy organizations is provided in Section XI.¹⁷⁰

123. Likewise, Purdue acknowledged in 2007 that it "[t]old PURDUE sales representatives they could tell health care providers that OxyContin potentially creates less chance for addiction than immediate-release opioids."

124. In my opinion, Purdue's marketing misleadingly claimed without substantial evidence that OxyContin was less addictive than competitor opioid products.

(d) Purdue Misleadingly Told Health Care Providers that Patients Exhibiting Signs of Addiction Were Likely "Pseudoaddicted" and in Need of Additional Opioids to Treat Pain

125. Pseudoaddiction is a term to describe a patient who appears "looking like a drug addict" but is instead in pain and displaying symptoms of pseudoaddiction, i.e., "misinterpretation of relief-seeking behaviors as drug-seeking behaviors." It is a term that Purdue's Dr. David Haddox claimed to have coined in 1988.¹⁷¹

¹⁶⁹ See, e.g., PKY180112501 at 11. This brochure, published by Purdue's unbranded organization, Partners Against Pain, repeated Purdue's conclusion that the rate of addiction was less than 1% based on this five-sentence letter, stating "[i]n fact, a survey of more than 11,000 opioid-using patients, taken over several years, found only four cases of documented addiction. ... Many patients—and family members—will be surprised to discover that fewer than 1% of opioid-using patients become addicted!" *Id.*

¹⁷⁰ Attachment B to Plea Agreement of U.S. v. The Purdue Frederick Co. Inc., Agreed Statement of Facts, PDD1712900035 at 6.

¹⁷¹ See PPLP003877027 at 9; Weissman, D. and J. Haddox. (1989). Opioid pseudoaddiction--an iatrogenic syndrome. *Pain*. 36(3): 363-66.

126. Pseudoaddiction is not supported by substantial evidence. In 2009, the American Pain Society and the American Academy of Pain Medicine, two pain advocacy organizations supported by Purdue, reviewed the claim of pseudoaddiction, finding:

We identified no systematic reviews or primary studies on accuracy of tools for differentiating drug-related behaviors due to inadequate symptom relief from true aberrant drug-related behaviors. The few studies that evaluated drug-related behaviors due to inadequate symptom relief in patients with chronic noncancer pain have not attempted to validate criteria for diagnosing this condition.¹⁷²

127. Prior to this, these and other pain advocacy organizations supported by Purdue published “educational” materials that recognized pseudoaddiction as a medical condition despite the lack of substantial evidence.¹⁷³

128. Often utilizing the materials published by these pain advocacy organizations, Purdue’s sales force promoted pseudoaddiction when physicians reported addicted patients or otherwise raised concerns about addiction to OxyContin.¹⁷⁴

128.1. April 9, 1998 (Ohio) - TALKED 3 APPROACH TO MOVING PAT OFF
OF S ACTING REM AND TOLER ACROCONT AND NO PROB WITH PH IE
ACID/ALKALINE SAME RELEASE EACH TIME. MUST TALK OXY KEYSARE
MORE PREDICTLEVELS VS ... AND REMIND HS DOSING AND PH INDEPEND
DELIV **SHOW HIM PSEUDO ADDICT AND NEED TO DOSE UP TO PAIN**
LEVEL SUGG FOR 6 PERCS LOOK AT RANGE AND INC DOSE ONE NOTCH¹⁷⁵

¹⁷² ENDO-OPIOID_MDL-01463855 at 102.

¹⁷³ See Section XI.

¹⁷⁴ A Purdue regional sales manager testified that a sales representative, when faced with a physician concerned about prescribing a higher dose of OxyContin because of addiction, should suggest the dose be adjusted upwards since the patient may be pseudoaddicted. Chris Sposato Dep. Tr. 145:5-147:19, Jan. 22, 2003, PDD9520404001.

¹⁷⁵ PPLPMDL0080000001 (emphasis added).

128.2. August 14, 1998 (Ohio) - F/U ON PHN PAT ON T3 3/DAY GO WITH 10-20 Q12H USING 10S **LOOK AT HIS CONCERNS DEA/ADDICTION REVIEW PSEUDOADDICT** SHOW MELNICK AND BROCHURE STRESS QOL AND PAT BENEFITS GOOD NIGHT REST ASK FOR 1 PAT GO AFTER OSTEO NEXT¹⁷⁶

128.3. November 2, 1998 (Ohio) - CONT TO ASK FOR OXY TO BE USED FOR NEW STARTS SHOW PKGE INSERT LESS ABUSE/SHOW BLOOD LEVELS PREDICT STRESS BEST PAIN MED ON MKT MOST PREDICT **ASK TO SWITCH PSEUDO ADDICTS TO OXY** WANTRING EARLY REFILLS CLOSE FORE THESE PAT¹⁷⁷

128.4. June 21, 1999 (Ohio) - **OXY ADDICTION VS PSEUDO**, DISEASE STATE MGT AND TITRATION ISSUES COPD AND UNI VS BID THEO¹⁷⁸

128.5. February 17, 2000 (Ohio) - obj: to find out what type pain patients she is treating with oxy Action: she is treating failed back patients for the most part she actually mentioned no longer treating patients with opioid therapy because she keeps getting dinged by patients seeking **we discussed pseudoaddiction vs addiction** as well as the OSMA book on pain and the 5th Vital Sign I left her with an opioid documentation kit-she is not sure her mind will be changed I mentioned if she is going to choose to use an opioid, oxy is the safest one to use¹⁷⁹

128.6. November 29, 2000 (Ohio) - he is so hungry for information-went over the comfort assessment journal and empowering hispatients to take more control of their

¹⁷⁶ PPLPMDL0080000001 (emphasis added).

¹⁷⁷ PPLPMDL0080000001 (emphasis added).

¹⁷⁸ PPLPMDL0080000001 (emphasis added).

¹⁷⁹ PPLPMDL0080000001 (emphasis added).

situation-as well as how hwe is assessinf **talked pseudo addiction physocological dependence** and proper titratiom of oxycontin gave his Coles Ten tips¹⁸⁰

128.7. December 1, 2000 (Ohio) - discussed one of his patients that he dismissed from the practice because of abuse-**we discussed the source of her pain and pseudo addiction as well as psycological dependence**-¹⁸¹

128.8. October 28, 2002 (Ohio) - issues here today as doing inservice are patients coming to them asking for oxycontin and **he feels they are selling it for \$80 / day** or more and just too tempting asked him what drug can he write that this can't occur **disc**... **pseudo addiction** and conntracts witih patient she feels better now...¹⁸²

128.9. October 17, 2003 (Ohio) - Gave Barrett and Marsa Columbus invite. Barrett pointed out Rush story. **Reminded him that under tx can = pseudo addiction and that if not good pain doc it can and will happen**. Marsa very rushed, but says he is using as 1st choice for po long acting.....¹⁸³

129. Purdue also created the pain advocacy organization, Partners Against Pain, which promoted pseudoaddictoin, among other claims about opioids.

129.1. In 2001, Partners Against Pain provided the following definition of pseudoaddiction in a "Pain Management Kit" that was distributed to healthcare providers: "Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may 'clock watch,' and may otherwise seem inappropriately 'drug

¹⁸⁰ PPLPMDL0080000001 (emphasis added).

¹⁸¹ PPLPMDL0080000001 (emphasis added).

¹⁸² PPLPMDL0080000001 (emphasis added).

¹⁸³ PPLPMDL0080000001 (emphasis added).

seeking.’ Even such behaviors as illicit drug use and deception can occur in the patient’s efforts to obtain relief.”¹⁸⁴ Partners Against Pain repeated this definition in the 2005 and 2007 versions of its “Pain Management Kit.”¹⁸⁵

129.2. In a Partners Against Pain 2007 “Defining Key Terms in Pain Management” document, the following definition was provided for pseudoaddiction: “Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may ‘clock watch,’ and may otherwise seem inappropriately ‘drug seeking.’ Even such behaviors as illicit drug use and deception can occur in the patient’s efforts to obtain relief.”¹⁸⁶

129.3. In its 2009 Pain Management Kit, Partners Against Pain stated that the following were “behaviors [are] less suggestive of an addiction disorder,” including “aggressive complaining about the need for more drug;” “drug hoarding during periods of reduced symptoms;” “requesting specific drugs;” “opening acquiring similar drugs from other medical sources;” and “unsanctioned dose escalation...”¹⁸⁷

130. Purdue likewise supported other pain advocacy organizations to make similar misleading claims about pseudoaddiction.¹⁸⁸

¹⁸⁴ PPLP003326602 at 56.

¹⁸⁵ PPLP004114967 at 4; PPLP003341378 at 1.

¹⁸⁶ PPLP003326602 at 56.

¹⁸⁷ PKY181695113 at 53.

¹⁸⁸ See Section XI.

131. In addition, Purdue's key opinion leaders were instructed on pseudoaddiction,¹⁸⁹ and gave presentations and otherwise conveyed the concept of pseudoaddiction to healthcare providers despite lacking substantial evidence to support the claim.¹⁹⁰

132. In my opinion, Purdue misleadingly told health care providers that patients exhibiting signs of addiction were likely "psuedoaddicted" and in need of additional opioids to treat pain.

(e) Purdue Minimized the Risks of Tolerance and Physical Dependence that Patients Could Experience with OxyContin

133. Known side effects of OxyContin include "tolerance" and "physical dependence."¹⁹¹

134. "Tolerance" is "the need for increasing doses of opioids to maintain a defined effect such as analgesia," and "physical dependence" is "the occurrence of withdrawal symptoms after abrupt discontinuation of a drug."¹⁹²

135. Both conditions "are not unusual during chronic opioid therapy."¹⁹³

136. Despite this, Purdue downplayed their risks in OxyContin promotional materials provided to health care providers. For instance, Purdue's sales representatives distributed reprints of a December 1998 article published by Robert Reder, MD, Purdue Vice President and Medical Director, and Sanford Roth, MD, a rheumatologist and speaker¹⁹⁴ for Purdue, which discussed the

¹⁸⁹ PDD1503981005 at 75.

¹⁹⁰ PDD1502210202 at 827 (identifying the speaker training presentation as "accredited continuing education").

¹⁹¹ SHC-000006346 at 4.

¹⁹² *Id.* see also Phillips JK, Ford MA, Bonnie RJ. (2017). Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. National Academies Press, *available at*: <https://www.ncbi.nlm.nih.gov/books/NBK458661/Phillips>.

¹⁹³ SHC-000006346 at 4 (emphasis added).

¹⁹⁴ See E513_00004803 at 9 (identifying Dr. Sanford as a speaker for a Purdue sponsored event); SHC-000024908 at 19 (identifying Dr. Sanford as a speaker at a Purdue symposium/luncheon).

“misconceptions” of opioids, including that “tolerance is rarely a practical problem in opioid therapy.”¹⁹⁵

137. Likewise, in promotional materials from 1996 through at least 2008, Purdue did not prominently disclose the possibility of tolerance or physical dependence to OxyContin.¹⁹⁶ Instead, Purdue focused primarily on the benefits of OxyContin.

137.1. For example, in or around December of 1996, Purdue sent to healthcare providers the following letter failed to present a fair and balanced evaluation of the risks and benefits of OxyContin by failing to disclose the possibility of tolerance or physical dependence to OxyContin:

On your formulary, q12h OxyContin can enhance pain control, because it provides:

- The analgesic efficacy of oxycodone* with the ease of q12h dosing
- Twelve hours of smooth and reliable pain control—less frequent dosing than with Percocet, Vicodin, or Tylenol with Codeine
- Analgesic onset within 1 hour in most patients
- Single-entity therapy—no aspirin or acetaminophen which may be potentially toxic in maximal daily doses
- No “ceiling” to analgesic efficacy—may be titrated upward when clinically necessary
- Diminishing side effects (except constipation) over time for many patients

OxyContin is a logical “next step” when around-the-clock (A-T-C) opioid therapy is needed. We are confident it is a logical “next choice” for your formulary.¹⁹⁷

¹⁹⁵ Sanford R. (1998). The Role of Opioids in the Treatment of Osteoarthritis. Resident & Staff Physician. 44(12):21-36, PDD1701869808.

¹⁹⁶ See, e.g., PURCHI-000550536; PURCHI-000723096; PURCHI-000723253; PURCHI-000723352; PURCHI-000723681; PURCHI-000723829; PURCHI-000723966; PURCHI-000724367; PURCHI-000763440; PURCHI-000813598; PURCHI-000830011

¹⁹⁷ PURCHI-000723253 at 70.

137.2. Similarly, the following September 18, 2003 promotional material used by Purdue as a display at a healthcare convention failed to present a fair balance of information relating to risks and benefits in that it did not prominently disclose the risks of tolerance and physical dependence to OxyContin.¹⁹⁸

For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time

THERE CAN BE LIFE WITH RELIEF

- **Q12h dosing convenience**
- **Onset of analgesia within 1 hour in most patients***
- **Convenient conversion and titration**
- **OxyContin® is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine. Consider this when an increased risk of misuse, abuse, or diversion is a concern**
- **OxyContin® Tablets are NOT intended for use as a prn analgesic**
- **OxyContin® TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin® TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE**
- **OxyContin® 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY.** These tablets may cause fatal respiratory depression when administered to opioid-naïve patients
- The most serious risk with OxyContin® is respiratory depression, which can be fatal
- OxyContin® is not indicated for pre-emptive analgesia, pain in the immediate postoperative period (the first 12 to 24 hours following surgery) in patients not previously taking OxyContin® (because its safety in this setting has not been established), or pain that is mild or not expected to persist for an extended period of time
- As used here, "moderate" and "moderate to severe" pain do not include commonplace and ordinary aches and pains, pulled muscles, cramps, sprains, or similar discomfort

* From a single-dose study.
Reference: 1. Sunshine A, Olson NZ, Colon A, et al. Analgesic efficacy of controlled-release oxycodone in postoperative pain. J Clin Pharmacol. 1996;36:595-603.

Q12h
OXYCONTIN® II
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS
IT WORKS

Please read professional prescribing information, including boxed warning, available at this exhibit.

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138. Purdue's pain advocacy organization, Partners Against Pain, also made statements that discussed the ability to increase the dose of opioids without adequately addressing the significant risk of doing so.¹⁹⁹

¹⁹⁸ PURCHI-000723966 at 19.

¹⁹⁹ Purdue also supported pain advocacy organizations that downplayed these risks. See Section XI.

138.1. A 2005 brochure titled “Clinical Issues in Opioid Prescribing” stated “[i]f opioid doses are gradually increased, high dosages are generally well tolerated and not associated with respiratory depression” without discussion of physical tolerance or dependence.²⁰⁰

138.2. Similarly, in the 2000 brochure titled “Counseling Your Patients and Their Families Regarding The Use of Opioids to Relieve Pain,” Partners Against Pain stated the following without discussing the associated risks with opioids “[u]nlike nonopioid pain relievers, an opioid has no “maximum” daily dose-which allows us to adjust the dose to an effective level, no matter how severe your pain” and “[r]emember, opioids are not limited to a ‘maximum’ dose as nonopioids are-an effective dose can be found for virtually any type or severity of pain.”²⁰¹

139. Even when Purdue acknowledged the risks of physical dependence in marketing OxyContin, Purdue downplayed their clinical significance. Specifically, Purdue minimized the severity of withdrawals symptoms resulting from physical dependence,²⁰² which per the OxyContin label, included restlessness, lachrymation, rhinorrhea, yawning, perspiration, chills, myalgia and mydriasis, among others.

139.1. In Purdue’s 1996 sales training, Purdue stated that tolerance and physical dependence do not pose a major clinical problems and that “it is usually not difficult to withdraw an opioid when it is no longer required,”²⁰³ which Purdue’s sales force conveyed to healthcare providers.

²⁰⁰ PPLP004114967 at 6.

²⁰¹ SHC-000024493 at 7, 9

²⁰² Purdue also supported pain advocacy organizations that downplayed these risks. See Section XI.

²⁰³ ABT-MDL-KY-0008846 at 63-64.

139.2. Purdue downplayed physical dependence and its associated withdrawal symptoms at a Purdue dinner symposium at the May 1997 convention of the National Association of Orthopedic Nurses. There, according to a summary provided by a Purdue sales representative, Elizabeth Narcessian, MD, “an active member of Purdue’s Speaker’s Bureau” who helped train other speakers as well as Purdue sales representatives,²⁰⁴ provided the following information to the 510 nurses in attendance about withdrawing from OxyContin:

Dr. Narcessian used an analogy that seemed to get across the addiction vs physical dependence issue. She said that if you drink coffee regularly and stop drinking it one morning, you will most likely get a headache (a withdrawal symptom). That is physical dependence, similar to the withdrawal effect experienced when an opioid is stopped.²⁰⁵

140. Purdue also misleadingly told healthcare providers without substantial evidence that “withdrawal symptoms” from physical dependence would not occur at lower doses but “when high dose opioid therapy is suddenly stopped,”²⁰⁶ such as at doses of 60 mg/day or higher.²⁰⁷

141. Since 1999, and possibly earlier, Purdue was aware reports of withdrawal symptoms in patients stopping OxyContin at doses less than 60 mg per day, and in as early as March 28, 2001, Purdue was aware of concerns regarding the accuracy of the withdrawal data in its published osteoarthritic study.

²⁰⁴ SHC-000024908 at 12.

²⁰⁵ PKY180254414 at 3.

²⁰⁶ Sanford R. (1998). The Role of Opioids in the Treatment of Osteoarthritis. Resident & Staff Physician. 44(12):21-36, PURCHI-000816988 at 21; *see also* Exhibit B to Plea Agreement of *U.S. v. The Purdue Frederick Co. Inc.*, Agreed Statement of Facts, at 9-13.

²⁰⁷ *Id.*; *see also* Sanford R. et al. (2000). Around-the-Clock, Controlled-Release Oxycodone Therapy for Osteoarthritis-Related Pain. Arch Intern Med. 160:853-860, PPLP003983624 at 7; *see also* Gasdia Dep. Tr. 248:16-22, June 27, 2008.

141.1. Purdue learned through a long-term clinical study evaluating OxyContin in osteoarthritis patients (Clinical Study OC92-1103) that physical dependence (and associated withdrawal symptoms) occur even at low doses. In this study, case report forms documented that 13 patients experienced symptoms of withdrawal during periods in which patients were instructed not to take OxyContin. Of the 13 patients, 3 withdrew during the respite period and were taking OxyContin doses less than 60 mg per day. Of the remaining 10 patients, all but two were taking doses lower than 60 mg per day.²⁰⁸ Purdue did not include these as instances of withdrawal in its final study report for OC92-1103, which it submitted to FDA on January 16, 1997.²⁰⁹

141.2. Approximately two years later, on February 12, 1999, an affiliate of Purdue²¹⁰ conducted a meta-analysis of the long-term clinical studies available for OxyContin, which included OC92-1103 and another Purdue clinical study, OC92-1101. This meta-analysis likewise identified instances of withdrawal in patients taking less than OxyContin 60 mg per day.²¹¹

141.3. After the issuance of this meta-analysis by a Purdue affiliate, Purdue—along with Dr. Sanford Roth and other clinical investigators—published the study results of OC92-1103 in a medical journal. In this published study, Purdue reported only two instances of withdrawal following abrupt cessation of doses of 60 mg/day or higher,

²⁰⁸ PPLPC024000037828 at 1-2 (identifying 3 subject who discontinued during respite because of adverse experiences due to possible withdrawal symptoms and additional 10 unique subjects who experienced adverse experiences due to possible withdrawal symptoms).

²⁰⁹ PURCHI-000566584.

²¹⁰ PKY180803001 at 8 (“Purdue Pharma LP, the US associate of Napp Pharmaceuticals Ltd.”).

²¹¹ *Id.* at 35-39.

which according to Purdue, “indicat[ed] that CR oxycodone at doses below 60 mg/d can be discontinued without tapering the dose if the patient's condition so warrants.”²¹²

141.4. Purdue utilized this published study to understate the risk of physical dependency and withdrawal; specifically:

On or about June 26, 2000, certain PURDUE supervisors and employees sent the full text of the osteoarthritis study article together with a “marketing tip” to PURDUE’s entire sales force. The marketing tip stated that a reprint of the osteoarthritis study article was available for use in achieving sales success. The marketing tip also included as one of the article's twelve key points: “There were 2 reports of withdrawal symptoms after patients abruptly stopped taking CR oxycodone at doses of 60 or 70 mg/d. Withdrawal syndrome was not reported as an adverse event during scheduled respites indicating that CR oxycodone at doses below 60 mg/d can be discontinued without tapering the dose if the patient condition so warrants.”²¹³

141.5. Purdue did not take affirmative action to correct this inaccurate information and continued to distribute reprints of the article to sales representatives, who in turn, distributed the false and misleading information to healthcare providers.²¹⁴

142. In my opinion, Purdue minimized the risks of tolerance and physical dependence that patients could experience with OxyContin.

(f) Purdue’s Marketing Minimized the Risks of Respiratory Depression, Addiction, and Abuse Associated with Higher Doses of OxyContin

143. From early market research, Purdue learned that physicians were concerned with prescribing opioid combination products, i.e., opioids combined with aspirin or acetaminophen

²¹² Roth S. et al. (2000). Around-the-Clock, Controlled-Release Oxycodone Therapy for Osteoarthritis-Related Pain. Arch Intern Med. 160:853-860, PPLP003983624 at 7.

²¹³ Attach. B to Plea Agreement of *U.S. v. The Purdue Frederick Co. Inc.*, Agreed Statement of Facts, PDD1712900035 at 12.

²¹⁴ *Id.* at 12-13.

such as Vicodin or Percocet, because “the toxicity limitation of the combination drugs ... precluded their use for the most severe pain, since it was not possible to give enough medicine to control the pain without putting the patient in danger.”²¹⁵ This “danger” was the concern of renal or hepatic toxicity from excess doses of aspirin or acetaminophen.

144. Purdue recognized that OxyContin, as a single-opioid agent, would not have this dose-limiting property, and in Purdue’s early market research, physicians identified “the absence of toxicity concerns as currently exist with the combination products” as an “important strength” of OxyContin and found “no dose ceiling” to be a “strong copy point” in which to market OxyContin.²¹⁶

145. Purdue highlighted this point in its promotion of OxyContin, telling physicians, for example, that “[a]s a single-entity opioid with no ceiling to analgesic efficacy, OXYCONTIN Tablets may be used at doses not limited by maximum permitted doses of NSAIDs or acetaminophen in fixed-combination products.”²¹⁷

²¹⁵ PKY181386644 at 27.

²¹⁶ *Id.* at 31, 34.

²¹⁷ PURCHI-00072320 at 24; *see also* PURCHI-00072310 at 13 (“Doses of opioid agonists such as oxycodone have no ceiling effect for analgesic activity, as evident in the wide dosage range of OXYCONTIN Tablets used in long-term clinical trials.”); *Id.* at 24 (“As a single-entity opioid with no ceiling to analgesic efficacy, OXYCONTIN Tablets may be used at doses not limited by maximum permitted doses of NSAIDs or acetaminophen in fixed-combination products.”); PURCHI-00072310 at 48 (“No ceiling to analgesic efficacy. With full agonists, such as oxycodone ‘effectiveness with increasing doses is not limited by a ‘ceiling.’ OxyContin may be dosed upward as clinically necessary.”); PURCHI-00072310 at 58 (“OxyContin has no ‘ceiling’ to its analgesic efficacy and may be titrated upward, when clinically necessary, with confidence.” (emphasis added)); PURCHI-000550536 at 38 (“Not limited by analgesic ‘ceiling’ or maximum daily dose. OxyContin may be dosed as high as clinically necessary.”); PURCHI-000672849 at 20 (“OxyContin may be titrated as high as clinically necessary, unlike analgesic products such as Percocet, Vicodin, Lorcet, Darvocet-N, and Tylenol with Codeine, or their generic equivalents. OxyContin can be titrated upwards every 24-48 hours, when clinically necessary, until an effective dose is reached, with acceptable side effects.”); PDD9316729260 at 67 (“There is added dosing flexibility with a single agent, since a variety of co-analgesics and adjuvant medications can be used to enhance the individual patient’s pain relief, while having the freedom to dose OxyContin Tablets as high as is clinically necessary.”); PURCHI-000701440 at 9 (“Consider the daily limitations. Many short-acting opioids contain a nonopioid analgesic that limits the maximum daily dose. OxyContin is a single-entity agent that does not contain acetaminophen, aspirin or ibuprofen. Ceiling to analgesic effectiveness is limited only by side effects.”).

146. In doing so, however, Purdue did not balance the significant risks associated with taking larger doses of OxyContin—namely, the potentially fatal risk of respiratory depression²¹⁸ and the increased risk of abuse.²¹⁹

147. Specifically, in marketing OxyContin, Purdue’s sales representatives emphasized that OxyContin has no dose ceiling, encouraging healthcare providers to increase the dose of OxyContin without discussing the risks associated with dose increases.

147.1. February 2, 1996 (Ohio) - BRIEFLY DISCUSSED OXY AND UNIMENTION. DISCUSSED WHO STEP APPROACH AND USE IN STEP 2 WITH OXYCODONE. AND ALSO USE IN NON MALIGNANT PAIN WITH LOWER ABUSE POTENTIAL. **STRESSED Q12H DOSING WITH OXY AND NO DOSE CEILING.** FOLLOW ON 2/12 WITH MORE DETAIL FROM PI ON OXY. FIND OUT WHERE HE SEES IT FITTING IN.²²⁰

²¹⁸ SHC-000006346 at 3; *see also* Phillips JK, Ford MA, Bonnie RJ. (2017). Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. National Academies Press, *available at*: <https://www.ncbi.nlm.nih.gov/books/NBK458661/Phillips>.

²¹⁹ *See* Dunn, K.M., et al., Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*, 2010. 152(2): p. 85-92; Gomes, T., et al., Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*, 2011. 171(7): p. 686-91; Bohnert, A.S., et al., Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*, 2011. 305(13): p. 1315-21; Paulozzi, L.J., et al., A History of Being Prescribed Controlled Substances and Risk of Drug Overdose Death. *Pain Med*, 2012. 13(1): p. 87-95; Zedler, B., et al., Risk Factors for Serious Prescription Opioid-Related Toxicity or Overdose among Veterans Health Administration Patients. *Pain Med*, 2014; Bohnert, A.S., et al., A Detailed Exploration Into the Association of Prescribed Opioid Dosage and Overdose Deaths Among Patients With Chronic Pain. *Med Care*, 2016. 54(5): p. 435-41; Dasgupta, N., et al., Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality. *Pain Med*, 2016. 17(1): p. 85-98; Bohnert, A., et al., Understanding Links among Opioid Use, Overdose, and Suicide. *N. Engl. J. Med* 2019; 380:71-9. In addition, Purdue acknowledged in 2001 that “[t]olerance to opioids which results in a dosage increase” was a “side effect” contributing to the abuse of OxyContin and that “[p]atients would therefore benefit from the reduction of the development of tolerance ...” (emphasis added).

²²⁰ PPLPMDL0080000001 (emphasis added).

147.2. March 6, 1997 (Ohio) - LIKES OXY BECAUSE OF FEWER SIDE EFFECTS. **STRESSED NO CEILING AND 80MG.** WILL SEND LIVE W/L²²¹

147.3. January 8, 1998 (Ohio) - USING OXY FOR OSTEO AL;SO STATING WITH PHN/DN **KEEP REM TO INC DOSE NO CEILING** REMIND QOL ADV AFTER NSAID UNIPH SHOW MARTIN TELL HIM CONVERS IS RIGHT TO DOSHOW QD BETTER THAN BIDID.²²²

147.4. January 20, 1999 (Ohio) - **MUST CONT TO STRESS ADV AND ABIL TO INC DOSE NO CEILING** WANTS A 60 MG DOSE SAID HAS MANY ON 20S/40S SUGG EITHER INTERVAL DOSING WITH 40S OR SWITCH TO 80MG Q12H²²³

147.5. February 9, 1999 (Ohio) - HE IS GOOD ON DOSING **HAS NOT EXCEEDED 80 Q12H YET CONTIN TO STRESS NO CEILING BUT SEEMS TO BE COMING AROUND ON THIS ISSUE** STILL FEELS TOLER IS SEEN BETWEEN 40-80 MG MUST....²²⁴

147.6. January 28, 2000 (Ohio) - MD ALWAYS SEES ME CARRYING IN SAMPLES OF SENOKOT WHICH STARTS CONVERSATION; MD SEEMS TO BE TRULEY THANKFUL FOR THE SAMPLES THAT HE RECEIVES; **OXY DISCUSSED RE: NO CEILING DOSE AND EASE OF TITRATION;** OXY

²²¹ PPLPMDL0080000001 (emphasis added).

²²² PPLPMDL0080000001 (emphasis added).

²²³ PPLPMDL0080000001 (emphasis added).

²²⁴ PPLPMDL0080000001 (emphasis added).

IR/FAST FOR BREAKTHROUGH PAIN; CONVERSION CHARTS LEFT WITH MD FOR HIS REVIEW.²²⁵

147.7. February 23, 2000 (Ohio) - Titration call again, went over no ceiling and that 80mg is far from too much. Dr said he gets the message and said he has used the 80mg.²²⁶

147.8. July 6, 2000 (Ohio) - SPOKE WITH MD WHO EXPRESSED CONCERN RE: ONE PT RECEIVING 120 MG Q 12 FOR BACK PAIN- DISCUSSED THE PFACT THAT THERE IS NO CEILING DOSE WITH OXY LIKE SHORT ACTING; HE SEEMED TO THINK THAT THIS PT WAS ABUSING THE PRODUCT; HE NEEDS REAFFIRMATION RE: THE DECREASED ABILITY OF OXY TO BE ABUSED AND DECREASING NUMBER OF TABS....²²⁷

147.9. August 11, 2000 (Ohio) - asked r to to upgrae to the 80 mg q 12 h for difficult pat - dr. agrees - positioned oxy ir for breakthrough reminder detail to dr. on oxy - stay w message - push the high dose - sampled uni and senokot reminded dr that 160 mg tab is coming out - he asked abt oxy fast for break - does not have in southside - y-town - disc high dose pat - 40 mg q 12 h asked if he would write oxy ins of ... for diff pat - disc the inconsist of pain control w ... - asked if he would write 80mg oxy instead of ... - said he will write more oxy f reminded dr that oxy has no ceiling - that he can go above 80 mg - also the potency of oxy vs vic is =n asked dr what he does after 40 mg q 12 - he adds ... - explained the no ceiling of oxy - told him 60 -80mg q 12 is a low dose

²²⁵ PPLPMDL0080000001 (emphasis added).

²²⁶ PPLPMDL0080000001 (emphasis added).

²²⁷ PPLPMDL0080000001 (emphasis added).

of a med that has no limits - says he will go up in dose before switching - was surprised to learn that oxy is no ceiling compared to combos - asked many q about hospice pat and nurses - wanted to know what chevlen does - lots of oxy - 1--1.5 ratio less hal and naus - fu on dosing up and acute vs vic.²²⁸

147.10. January 19, 2001 (Ohio) - doc said he has been using oxy for awhile and that he uses high doses, **i reminded doc there is no ceiling and that he should not worry about how high he needs to go.**²²⁹

147.11. April 6, 2001 (Ohio) - OK w Oxy has (post op back) pt on 80mgs q 12h with Oxy IR q4 in between, talked about titrating up to 100mgs q12 h, at first said he was going to refer to Dr Chevlen, **thinks something else may be going on afraid of higher doses- told of no ceiling,** pt is coming in next week, hopefully he will give this a try before referral. Invited to Dr G's RT but staff doubtful if he will attend because he frequently works until 7:00pm.²³⁰

147.12. March 20, 2003 (Ohio) - Spoke with Dr in clinic, **Dr asked me about a max dose with OxyContin. I went over the idea of no ceiling with any single entity drug and that what actually limits combos is acet and apap.** I explained the advantage of being able to titrate to effect with out worry of acet or apap toxicity.²³¹

148. According to depositions of Purdue employees, Purdue generated greater revenue off the higher doses of OxyContin,²³² and Purdue encouraged its sales force to promote higher

²²⁸ PPLPMDL0080000001 (emphasis added).

²²⁹ PPLPMDL0080000001 (emphasis added).

²³⁰ PPLPMDL0080000001 (emphasis added).

²³¹ PPLPMDL0080000001 (emphasis added).

²³² Sposato Dep. 18:21-24, PDD9520404001.

doses of OxyContin by utilizing a unique incentive system that bonused sales representatives based on increasing dollar volume of sales and not on the number of prescriptions written as is the usual practice.

148.1. As explained by Karen White, a sales representative for Purdue from 1998 to 2002, bonusing on the increase in dollar sales meant “[i]t would exponentially affect our bonuses. I mean if we got the doctor, as I mentioned earlier, to write an 80 milligram instead of a 10 milligram, we would make seven and a half times more money based on what percentage of our sales that we increased over our quota.”²³³

148.2. As a result of this incentive structure, according to Ms. White deposition testimony, sales representatives were encouraged to call on pill mills:

[T]he other reason that I have a problem with [the incentive structure] it is that it behooved us to call on what I refer to as pill mill doctor, doctors who are inappropriately prescribing narcotics. If a Purdue representative knew from one source or another that a doctor was inappropriately prescribing and was a pill mill, a lot of times they didn't turn them in to Purdue because they were making tons of money off of these doctors prescribing OxyContin in the place of other medications. And they were typically prescribing high doses of OxyContin in a lot of cases.²³⁴

148.3. Ms. White's testimony is further supported by a 2001 internal sales memo in which Purdue highlighted to sales representatives that they should “[f]ocus on high prescribers ~ 2-4 calls per month.”²³⁵

149. In my opinion, Purdue's marketing minimized the risks of respiratory depression, addiction, and abuse associated with higher doses of OxyContin.

²³³ White Dep. 98:23-99:14, Dec. 17, 2003, PKY182895039; *see also* Sposato Dep. 18:21-19:2, PDD9520404001. (“Q. My question is: Same amount of pills, higher dosage, Purdue makes more money for the higher dosage, correct? A. That's correct. Q. And that factors into someone's bonus, correct? A. Possibly.”).

²³⁴ White Dep. 99:15-25, PKY182895039.

²³⁵ ABT-MDL-KY-0050021 at 5.

2. In Response to OxyContin Not Being Effective for 12 Hours, Purdue Developed a Strategy to Increase the Total Daily OxyContin Dose but Failed to Inform the Public, Putting Patients at Risk.

150. Based on its pre-market research, Purdue's Marketing Department reported that OxyContin would be positioned as "the only opioid combining the efficacy and safety of oxycodone with the convenience of 12-hour dosing schedule."²³⁶

151. In Purdue's clinical trial program, OxyContin did not provide 12 hours of pain relief for most patients. Specifically, in the majority clinical trials in which rescue dosing was permitted, more than half of the subjects required daily rescue dosing for the majority of treatment time.

151.1. For example, in OC92-1001, which was a double-blind, randomized, q12hr multiple-dose, parallel-group comparison of the pharmacokinetic and pharmacodynamic profiles of controlled-release oxycodone (OxyContin) and MS Contin tablets in patients with chronic cancer-related pain, "rescue use was quite infrequent (an average of one dose per day)."²³⁷ It is important to note that MS Contin was considered a Q8-Q12 hr drug. In other words, on average, 50% of the doses in both arms of this study failed.

151.2. Similarly, in OC92-1201, titled A Double Blind, Randomized, Two-Period Crossover Comparison of the Pharmacokinetic and Pharmacodynamic Profiles of Immediate-Release and Controlled Release Oxycodone in Patients with Chronic Low

²³⁶ PPLP004030214 at 1, 9.

²³⁷ PURCHI-000543673 at 28.

Back Pain, “patients required, on average, approximately 0.6 doses per day” of rescue medication.²³⁸

151.3. Similarly, in OC93-0303, titled Double-Bind, Randomized, Repeated Dose, Crossover Comparison of The Pharmacokinetic and Pharmacodynamic Profiles of Controlled-Release Oxycodone and Controlled-Release Morphine in Cancer Patients with Pain, which compared OxyContin to MS Contin in cancer patients, “the mean number of rescue doses taken by patients ... was significantly higher with CR oxycodone compared with CR morphine for the 3-day average.”²³⁹ Specifically, in this study, the OxyContin patients reported using an average of 1.43 rescue doses during the last three days of the double-blind period of the study.²⁴⁰

151.4. In OC96-0204, titled “An Open-Label Multi-Center Study to Confirm the Guidelines for the Conversion of OxyContin Tablets when Utilized for the Conversion of Post-Surgical Subjects from Intravenous Continuous Opioid Infusion (CI) and/or Patient Controlled Opioid Analgesia (PCA) to an Oral Controlled Release Oxycodone Regimen” “patients used an average of 1 dose of supplemental analgesic daily” following implementation of the OxyContin.²⁴¹

151.5. In another clinical trial, OC91-0402A, which compared OxyContin to immediate release oxycodone in patients previously stabilized on strong opioid analgesics for chronic cancer-related pain, the protocol did not permit the use of rescue dosing among patients, leading to a discontinuation of 9 of 42 (21%) OxyContin patients.

²³⁸ PURCHI-000599520 at 64.

²³⁹ PURCHI-000564151 at 68.

²⁴⁰ *Id.*

²⁴¹ PURCHI-000627156 at 5.

Among patients on the comparator arm, 4 of 36 (11%) patients were discontinued for rescue dose.²⁴²

151.6. In a similar study, OC91-0402B, rescue dosing due to ineffective treatment was not initially permitted and any patient requiring rescue medication would be discontinued from the study. “A total of 36 out of 81 (44.4%) randomized CR patients discontinued from the study: 18 (22.2%) for ineffective treatment.”²⁴³ The clinical trial protocol was then amended, and “[p]atients enrolled after Amendment II were allowed titration prior to entry into double-blind and rescue medication. With this availability the discontinuation rate due to ineffective therapy for patients receiving CR Oxycodone dropped to 3.5%.”²⁴⁴ “The overall number of rescues doses per day was 0.6 for the CR Oxycodone group...”²⁴⁵ In other words, on average, more than half of the OxyContin doses failed.

151.7. In reviewing these clinical trials, the FDA Medical Officer Review noted that “[i]mmmediate release oxycodone was used as the rescue analgesic [sic] in these studies . . . Patients used about 1-2 doses of rescue a day and found it an important part of therapy.”²⁴⁶

152. Even though Purdue’s clinical trial program demonstrated that OxyContin, absent rescue dosing, could not provide continual analgesic relief on a Q12h basis in most patients, Purdue acknowledged that prescribing OxyContin on a dosing regimen less than Q12h could

²⁴² PURCHI-000587719 at 209.

²⁴³ PURCHI-000591935 at 36.

²⁴⁴ *Id.*

²⁴⁵ *Id.* at 98.

²⁴⁶ PURCHI-000667209 at 53.

jeopardize OxyContin's position with insurance formularies who would give preference to generic opioid products at those dosing frequencies.

152.1. In a June 6, 2000 email, Purdue's Robert Vik wrote that he was "informed that a growing number of patients are being prescribed OxyContin on a Q4h – Q8h frequency. This has precipitated a serious discussion by the HMO as to whether OxyContin should be prior authorized. As you know, a restriction of this magnitude can *greatly impact sales.*"²⁴⁷

152.2. Purdue's Phil Cramer replied to this email, stating that Purdue "must take a hard line in promoting OxyContin q12h...Q12-Q8-Q6-Q4 is no longer 'just' a matter of using the drug appropriately and effectively. **This issue is also critical to keep OxyContin available and reimbursible [sic] by MC plans and by PBM's!**"²⁴⁸

152.3. Similarly, in a July 25, 2001 sales training presentation titled "QxyContin q12h Workshop," promotion of OxyContin "as a true q12h drug" was needed to "differentiate OxyContin from MS Contin and other long-acting morphines," which are dosed Q8h or Q12h, otherwise "the rationale to keep [OxyContin] on hospital and MCO formularies is gone."²⁴⁹

152.4. In this same presentation, Purdue addressed "[w]hy is q12h so important," explaining:²⁵⁰

²⁴⁷ SHC-000006498 (emphasis added).

²⁴⁸ SHC-000006498 (emphasis added).

²⁴⁹ PPLP003996972 at 4.

²⁵⁰ PPLP003996972 at 1, 6.

Why is q12h Dosing So Important?

- Managed care companies are denying or will start denying shorter prescriptions
- Pharmacies may refuse to fill any Rx that is otherwise
- Increased FDA/DEA oversight
- Proper dosing minimizes diversion and abuse

152.5. Purdue also acknowledged in this presentation that prescribing OxyContin Q8h “is not malpractice” and would be “within the prescribing guidelines for titration”.²⁵¹

The Reality

- Although within the prescribing guidelines for titration, q8h is not within the recommended dosing guidelines.
- This is not malpractice, and we should never suggest that the physician could be held accountable for prescribing outside the package insert.
- Refocus the clinician back to q12h dosing with a complete explanation of the AcroContin™ delivery system and the importance of maintaining that dosing schedule.

153. Despite this, Purdue instructed its sales representatives to aggressively discourage healthcare providers from prescribing OxyContin on a less than Q12h basis and instead encourage them to increase the dose of OxyContin.

²⁵¹ PPLP003996972 at 10 (emphasis added).

153.1. In a July 18, 1999 document titled “What’s the OxyContin Message?” Purdue provided sales representatives a response to a doctor who “doesn’t believe it [OxyContin] works 12 hours,” stating that OxyContin Q12h was tested in “713 pts [patients] preNDA – Q12 at right dose is right dose.” This response failed to disclose the need for rescue dosing in the clinical trial.²⁵²

153.2. In a memo on January 20, 2000 distributed to the South Western Region sales representatives, the issue of Q12H versus Q8H was addressed. Sales representatives were told they “need to make sure that we are fighting the good fight for the patients, and sell OxyContin Q12H with conviction.” If doctors were prescribing OxyContin Q8h, the memo instructed sales representatives to “challenge [prescribers] to better assess their patients,” noting “the dose may not be high enough during the day.”²⁵³

153.3. In the July 25, 2001 sales training presentation discussed above, Purdue told sales representatives that “[t]his is an extremely important topic for the company right now. All managers and representatives must remember the **“BIG PICTURE”** when it comes to OxyContin. We cannot be afraid to address dosing other than Q12h with clinicians because we fear a drop in sales. It is imperative clinicians know where we, as a company, stand on this issue.”²⁵⁴

153.4. Similarly, in a Purdue sales training document titled “Q12h vs. Q8h Warfare,” sales representatives were told, “[t]he action of adding a dose, as opposed to increasing the Q12h dose, needs to be nipped in the bud. NOW!!.”²⁵⁵ They were further

²⁵² SHC-000008102 at 2.

²⁵³ PPLP003996839.

²⁵⁴ PPLP003996972 at 2.

²⁵⁵ PPLP003996830

advised that “the war is on – OxyContin is a true 12h product. Help the MD see that 12h is appropriate dosing for the patient controlling the pain, enhancing quality of life, even if it means using an escalating dosage and number tablets.”²⁵⁶

153.5. This sales training document encouraged sales representatives to focus physicians on titrating upwards the dose of OxyContin rather than changing the dosing frequency, commenting that increasing the dose would “result in a bigger bonus for us!!.”²⁵⁷

154. In accordance with Purdue’s directives, Purdue’s sales representatives discouraged healthcare providers from dosing OxyContin less than Q12h and encouraged them to instead increase the dose upwards.²⁵⁸

154.1. March 6, 1997 (West Virginia) - “HE IS 76% OXYCONTIN, BUT HE STIL IS DOSING IT Q8 FOR SOME PATIENTS, I EXPLAINED HOW THE CURVES WOULD OVER LAP AND OVER A PERIOD OF TIME ACCUMULATE. **I EXPLAINED IF IT WASN'T LASTING 12 HOURS, HE SHOULD IN- CREASE THE DOSE.** THE PAIN COULD HAVE INCREASED OR THEY COULD BE UNDER DOSED.”²⁵⁹

²⁵⁶ *Id.*

²⁵⁷ *Id.* (emphasis added).

²⁵⁸ Purdue was aware through early testing that prescribers were not dosing in accordance with package insert. In a January 4, 1994, Project Team Contact Report between Purdue and the FDA discussing “OC93-0704 – Package Insert Testing Study,” one of the results found was that “one half of the physicians did not dose according to the package insert.”²⁵⁸ The following year, Purdue learned that a one-time Purdue clinical investigator was conducting a study using Q8h. Rather than encourage the development of data on Q8h dosing, Robert Reder, M.D., Purdue’s Vice President, Medical Director sent a letter on July 24, 1995 to the clinical investigator, stating that “this situation concerns me as OxyContin has been developed for q12h dosing only (see draft package insert). In order to develop accurate information on alternative dosing schemes, proper controlled studies would need to be conducted. Because such studies have not yet been performed, I request that you not use a q8h dosing regimen.” SHC-000007900

²⁵⁹ PKY182404281 (emphasis added).

154.2. May 12, 1997 (New Jersey) - **PTS MOSTLY ON 20 Q8** SHE'S EASY TO TALK TO AND I ASKED IF THAT'S THE DOSE HOW DO YOU TITRATE OH SOMETIMES JUST ADD ANOTHER PILL AT NIGHT OR IN AM, **THIS IS EASIEST WAY INCREASE DOSE AT Q12 DON'T SHORTEN TIME** THEN INCREASE BY 50% EVERY 24 HRS WHEN STABLE MOVE TO NEXT TAB SIZE²⁶⁰

154.3. August 4, 1998 (New Jersey) - "A SLEW OF PROBLEMS W/ OXY FROM **NOT LASTING 12 HRS** TO SEVERE CONSTIPATION, AFTER A SERIES OF? HE'S NOT DOSING HIGH ENOUGH AT Q12 AND THEY DON'T START A LAXATIVE UNTIL PT IS CONSTIPADNEXT START AT BASICS"²⁶¹

154.4. February 22, 1999 (Ohio) - "PATIENT AT PHARM IN DAYTON HAVING PROBLEMS-**40MG Q8HR SHE BELIEVES THE PATIENT**"²⁶²

154.5. March 30, 2000 (West Virginia) - "**sd oxy is not lasting 12 hrs. dr dosing 20 q12. pted out needs to increase a little hihger and use the 10 mg tabs.** dr sd also has a lot of chronic pain pts. usually uses ultram tyl 3 or hydrocet. gave and disc caldwell and reminded of dosing convenience lower se's as demonstrated in paper. ncp: chronic pain .. lower abuse pot"²⁶³

154.6. November 13, 2001 (New Jersey) - "Vidaver starts everyone **on q12h and then when needs to titrate he puts them on q8h so he doesn't have to write for 2 different strengths**. I went over 3-2 rule in order to avoid this and keep pt. on q12h. Dr.

²⁶⁰ PKY182317787 (emphasis added).

²⁶¹ PKY182331401 (emphasis added).

²⁶² PKY182144588 (emphasis added).

²⁶³ PKY182418949 (emphasis added).

Haliczer - is putting most everyone on q8h No breakthru neither is Vidaver They believe pts have too much problem w/ IR meds and goal of long-acting is to avoid addictive potential w/ popping pills all day. and w/o breakthru pts. are saying it's not lasting long enough”²⁶⁴

154.7. July 15, 2002 (New Jersey) - “**Polcer said writes some Q12 and some Q8 said its not always lasting 12 hours** went over indication and package insert and titration Went over the PPI said it will be helpful but too much info for pt sometimes confuses them or leads them to believe they are having side effects that they aren't really having I pointed out that the PPI has bold print of to be swallowed whole”²⁶⁵

154.8. May 19, 2010 (Ohio) - You went in with the goal of finding out how she utilizes her short-acting opioids. **You never got to this as she began telling you about a patient taking 80mg q12h that is not lasting 12 hrs. and how she is supplementing with OxyContin 20mg two hours after the 80mg dose.** You explained to her that OxyContin is only indicated for q12h dosing and there is no data to support anything other than this dosing. You handled this correctly.²⁶⁶

155. In my opinion, Purdue developed a strategy to increase the total daily OxyContin dose but failed to inform the public and put patients at risk in response to OxyContin not being effective for 12 hours.

3. Purdue Overstated the Benefits of OxyContin with Respect to Sleep, Work, and Physical Activity and Leisure

156. Prior to the approval of OxyContin, Purdue submitted OxyContin promotional launch materials for FDA review. These materials included claims that OxyContin improved a

²⁶⁴ PKY182212989 (emphasis added).

²⁶⁵ PKY182178532 (emphasis added).

²⁶⁶ PPLPMDL0020000002 (emphasis added).

patient's quality of life; specifically, that "patients reported that OxyContin did not impair their ability to...sleep, walk, perform normal work, enjoy life, get along with other people."²⁶⁷

157. While substantial evidence existed to support these quality life claims when comparing OxyContin to placebo, Purdue lacked evidence to support these quality of life claims as compared to to other opioid products, which FDA noted on January 31, 1996 stating that "this claim would be misleading because it fails to disclose that these improvements were in comparison to placebo only."²⁶⁸

158. In response, Purdue corrected its promotional materials on February 9, 1996 to highlight that its quality of life claims for OxyContin were "relative to placebo."²⁶⁹

159. Nonetheless, in sales training and promotional materials, Purdue did not tell healthcare providers that OxyContin resulted in an improved quality of life *as compared to placebo*—a claim it lacked substantial evidence to make.

159.1. For instance, in a November 4, 1996 memo from Training and Development to the Entire Field Force on planning an effective sales presentation, Purdue's Jim Lang recommended that sales representatives tell doctors that "OxyContin can provide pain relief to your patients, allowing them to sleep through the night, while potentially creating less chances for addiction than immediate-release opioids."²⁷⁰

²⁶⁷ PURCHI-000622714 at 13. On a January 11, 1996, Purdue resubmitted promotional materials to FDA that revised the quality of life claims, stating "OxyContin 20 mg q12h...significantly decreased pain, improved quality of life, mood and sleep." PURCHI-000622986.

²⁶⁸ PURCHI-000623100 at 1-2.

²⁶⁹ PURCHI-000623112 at 7, 20, 43 (emphasis added).

²⁷⁰ SHC-000003754 at p. 2.

159.2. In addition, in January 2000 training materials, Purdue provided sales representatives a pamphlet that described OxyContin as “[i]mprov[ing] quality of life, mood, and sleep.”²⁷¹

159.3. In 2001, a second version of a promotional video entitled, “I Got My Life Back: Patients in Pain Tell Their Story,” Purdue presented stories of patients who had taken OxyContin and included unsubstantiated quality of life claims.²⁷²

160. Purdue’s sales representatives proceeded to tell healthcare providers that OxyContin was proven to improve a patient’s quality of life as compared to other opioid products without substantial evidence:

160.1. March 4, 1996 (Ohio) - HUGE PERCO WRITER, **POSITIONED AGAINST Q4H DRUGS AND QUALITY OF LIFE**, WAS UNCERTAIN REGARDING STARTING DOSES, SHOWED EQUI DOSES CERTAIN PATIENTS.²⁷³

160.2. July 10, 1996 (Ohio) - WORKING W PAM TO GET MORE PAT'S CONVERTED. **THEY USE ALOT OF PERC AND THERE IS NO REASON FOR NOT USING. SLEEP AND QUALITY OF LIFE ARE IMPORTANT ISSUES AND SHOULD BE FOCUSED UPON.**²⁷⁴

160.3. September 9, 1996 (Ohio) - SHOWED OXY VISUAL. STRESSED FAST ONSET, BETTER COMPLIANCE AND LESS ABUSE THAN COMBOS THEY ARE USING WILL TRY. **QUALITY OF LIFE AND SLEEP** NT.²⁷⁵

²⁷¹ PKY180261022 at 6.

²⁷² U.S. Government Accountability Office, *Prescription Drugs: Oxycontin Abuse and Diversion and Efforts to Address the Problem*, GAO-04-110 (Washington, DC, December 2003) at 32-33.

²⁷³ PPLPMDL0080000001 (emphasis added).

²⁷⁴ PPLPMDL0080000001 (emphasis added).

²⁷⁵ PPLPMDL0080000001 (emphasis added).

160.4. January 29, 1997 (Ohio) - T2 DR.CORTESE HE WAS CONCERNED WITH THE COSTS.OF OXY. HE SAID THAT HE STARTS WITH VICODIN,THEN TO PERCOCET,AND THEN TO OXY OR MS-CONTIN OR ... NTXC:MENTION HOW EXPENSIVE DURAGES IS IN COMPARISON TO EVERYTHING ELSE PUSH OXY ON ALL FORMULAR AND MEDICAID, **ALSO STRESS PT QUALITY OF LIFE**. Q12H DOSING VS Q4-6H DOSING USE START W/STAY W/AND GAIN EARLIER USE **VS.COMBOS**.²⁷⁶

160.5. February 5, 1997 (Ohio) - TD2 DR.ABOUT CESSATION OF THERAPY AND HE SAID THAT SOME OF THOSE PTS.REQUEST CERTAIN PRODUCTS.I ALSO SHOWED OSA STUDY IN PI AND 18 MONTH STUDY FOR OA PTS.I TALKED TO ABOUT COMBOS NTXC:BE MORE SPECIFIC ON THE PT TYPE TO **LOOK FOR VICODEN, T3, OR PERCOCET PTS AND CLOSE WITH QUALITY OF LIFE FOR THE PT**.ON Q12H DOSING VS.Q-4-6DOSING& COVER INS.COVERAGES&COSTS.²⁷⁷

160.6. February 6, 1997 (Ohio) - TD2 DR.GILBERT HE SAID THAT HE WOULD TRY OXY ON A FEW PTS. TO SEE HOW IT WORKS. HE LIKED THE FACT OF NO APAP OR ASA & LONG ACTION VS. SHORT ACTION AND CESSATION OF THERAPY.WE TD' ABOUT UNI AND COPD PTS.NOCTURNAL SYMPTOMS AND ASKED FOR NEW UNI STARTS NTXC:ASK IF HE HAS STARTED ANY NEW PTS.ON OXY & **REPOSTION IT INPLACE OF COMBO'S AND PT QUALITY OF LIFE INCR.**²⁷⁸

²⁷⁶ PPLPMDL0080000001 (emphasis added).

²⁷⁷ PPLPMDL0080000001 (emphasis added).

²⁷⁸ PPLPMDL0080000001 (emphasis added).

160.7. September 30, 1997 (Ohio) - WENT OVER SUNSHINE POST OP STUDY. USING DARVOCET, VICODIN PERCOCET. HIT DELIVERY SYSTEM, IMPROVED QUALITY OF LIFE. FOLLOW UP WITH Q12 DOSING.²⁷⁹

160.8. February 12, 1998 (Ohio) - DR SEES ALOT OF GERIATRIC PATIENTS, AND COPD PATIENTS.HIT OXYCONTIN NOMALIGNANT USE, USED PI TO SHOW CONVERSIONFACTORS OF HYDROCODONE AND OXY. PI FOR LESS FREQUENT DOSIG AND IMPROVE QUALITY OF LIFE.UNI, HIT QD WITH IMPROVED PULM FUNCTION PEAKING IN THE AM.²⁸⁰

160.9. April 15, 1998 (Ohio) - DR USES PERCODAN, HIT OXY WITH DELIVERY SYSTEM, LESS FREQUET DOSING, IDEA OF IMPROVEMENT IN QUALITY OF LIFE, NOT TOTAL PAIN CONTROL. QUICK ONSET OF ACTION WITH Q12 DOSING.²⁸¹

160.10. August 6, 1998 (Ohio) - “OXY FOR ALL VIC PTS/LESS ABUSE POTENTIAL AND PTS CAN SLEEP THROUGH PM.”²⁸²

160.11. January 5, 2000 (Ohio) - Advantage of using Oxy vs Percocet for chronic pain, quality of life issues. B.O./ Sit-down call. Seems to have Oxy niched on third step, after NSAIDS & short-acting combos. Discussed Oxy as one to “Start/stay with”. No need to go to combos, patients then has to clock watch. With Oxy, prevent

²⁷⁹ PPLPMDL0080000001 (emphasis added).

²⁸⁰ PPLPMDL0080000001 (emphasis added).

²⁸¹ PPLPMDL0080000001 (emphasis added).

²⁸² PPLPMDL0030008507 at 1 (emphasis added).

rather than manage pain. 12 hour smooth blood levels for A-T-C pain control. Oxy Wall conversion chart & titration guide.²⁸³

160.12. March 1, 2000 (Ohio) - Pain the 5th Vital sign, page 16. Stay on recommendation of long-acting opioids. Inquired about patients he has known for a long time, trusts. Those are the patients that would be excellent candidates for Oxy. **The elderly patient who has been taking T-3, hydrocodone, darvocet etc. Quality of life issues for them....sleep thru the night, rested during the day.**²⁸⁴

160.13. October 16, 2000 (Ohio) - **introduced oxy for use in place of short acting** usually t-3 or vicodin discussed side effects and dosing use po5 c-asked forrx **discussed quality of life** and better pain control senokot for side effects c-asked for rx.²⁸⁵

160.14. December 4, 2001 (Ohio) - gave linda titration pamphlet **focusing on quality of life with long acting vs short acting agent** when pt fits indication for oxycontin POA: need to share aps guidelines re short acting agents when linda has more time.²⁸⁶

160.15. April 30, 2003 (Ohio) - lecture dinner--explained oxycontin q12h, **dr clinton had talked about quality of life, so I mentioned keeping highest quality with q12h dosing**, titration every 1-2 days. also remind senokot. need to take CE brochures to fellows room and new titration g lecture dinner....²⁸⁷

²⁸³ PPLPMDL0080000001 (emphasis added).

²⁸⁴ PPLPMDL0080000001 (emphasis added).

²⁸⁵ PPLPMDL0080000001 (emphasis added).

²⁸⁶ PPLPMDL0080000001 (emphasis added).

²⁸⁷ PPLPMDL0080000001 (emphasis added).

160.16. July 30, 2007 (Ohio) - “discussed use of low-dose Oxycontin & where it fits w/ patients in his practice. Tied together use of assessment guide w/ low-dose 10mg to reduce pain & improve functionality. Doc said he has a couple of patients who could benefit from this”²⁸⁸

161. In addition, Purdue’s key opinion leaders gave presentations and otherwise conveyed that OxyContin improved patients’ quality of life without clarifying that this claim was valid only as compared to placebo.²⁸⁹

162. Likewise, Partners Against Pain, Purdue’s pain advocacy organization, claimed that opioids improved a patient’s quality of life without stating that this comparison was only valid as to placebo only.²⁹⁰

163. In my opinion, Purdue overstated the benefits of OxyContin with respect to sleep, work, and physical activity/leisure.

4. Purdue Promoted OxyContin for Indications that Were Broader than Supported by Substantial Evidence and for Which Safety and Efficacy Were Not Established

164. OxyContin has never been expressly approved for the use in osteoarthritic pain, lower back pain, or post-operative pain nor has OxyContin been approved for the use of all pain or even mild pain.²⁹¹

²⁸⁸ PPLPMDL0020000001 (emphasis added).

²⁸⁹ PDD1501606099 at 40; *see also* PDD8801245481 (list of paid Purdue speakers).

²⁹⁰ SHC-000024493 at 5 (“Pain-free patients are a help, not a hindrance to the treatment of the primary disease. With pain under effective control patients enjoy a better quality of life. They can eat, sleep, perform daily activities more normally.”) Purdue also supported pain advocacy organizations that downplayed these risks. *See* Section XI.

²⁹¹ *See* Section XI.

165. The initial OxyContin label referenced in the Clinical Trial section three non-malignant pain studies—one involving osteoarthritis pain, another involving lower back pain, and a third post-operative study.

166. The inclusion of these non-malignant pain studies in the OxyContin label was described by Purdue in a 1996 Purdue Research Center report as “so valuable”²⁹² with Purdue noting “our package insert team ... did its job skillfully” because the OxyContin label “contain[ed] all the major elements of our long-range marketing platform for [OxyContin]” despite FDA’s Curtis Wright stating “that all of this promotional material would disappear.”²⁹³

167. Despite the references to the non-malignant pain studies in the package insert, FDA told Purdue on multiple occasions that OxyContin should not be used in these patient populations.

167.1. In a March 19, 1993 teleconference, FDA Medical Reviewer, Dr. Curtis Wright, told Purdue that “there were very strong opinions of members at the FDA that opiates should not be used for non-malignant pain,”²⁹⁴ a labeling claim for osteoarthritis would be “strongly resisted,” and that long-term use in osteoarthritic patients was believed to be “unwarranted” by individuals at FDA.²⁹⁵

I met with Dr. Wright to discuss the osteoarthritis protocols OC 92-1102 and OC 92-1103. Dr. Wright provided me with some information on Oxaprozin (attached) to show the pitfalls of OA studies. Dr. Wright had both general and specific comments on the protocols. **Of greatest**

²⁹² PKY180673220 at 10.

²⁹³ PKY180673220 at 3.

²⁹⁴ PPLP004030167 at 11.

²⁹⁵ SHC-000002018 at 1. With respect to Purdue’s decision to study OxyContin in osteoarthritis patients (clinical study OC 92-1102), Dr. Wright recommended that Purdue “rewrite the introduction to OC 92-1102 to make it clear that osteoarthritis is being used as a pain model and that Purdue Frederick recognizes single-entity opiate use is not appropriate except in highly selected subpopulations.” *Id.*

importance is the fact Dr. Wright said that for certain individuals in the division and in the agency, the use (i.e., long term) in osteoarthritis is unwarranted. The way the protocols are written, it looks as if Purdue Frederick is attempting to obtain labeling claims for pain from osteoarthritis. This will be strongly resisted. He suggested that we chop the extension protocol (OC 92-1103) and rewrite the introduction to OC 92-1102 to make it clear that osteoarthritis is being used as a pain model and that **Purdue Frederick recognizes single-entity opiate use is not appropriate except in highly selected subpopulations.** If we wish to perform a long-term study in osteoarthritis patients, **we should study highly selected patients. Such as study should include questionnaires and data collection directed toward abuse, evaluation of diversion,** increase use with time (tolerance), efficacy and safety. Clinicians as well patients as well as patients must be questioned.²⁹⁶

167.2. In the FDA's Medical Officer Review of OxyContin from May 3, 1995, the FDA Medical Officer confirmed that Purdue did not have the data to support use in osteoarthritis patients, stating "this data is not adequate by itself to support an OA indication, but [OC 92-1102] is a very helpful trial in a non-oncologic chronic pain model."

167.3. Similarly, a review by the FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) of OxyContin promotional materials in December of 1995 resulted in FDA stating that it would not be appropriate for Purdue to reference results the clinical study in post-operative pain patients. In a letter to Purdue, DDMAC wrote that "by referencing this one single-dose study in post-operative patients, it implies that OxyContin is indicated for this patient population." DDMAC recommended that if Purdue wished to use this study "the introduction be qualified by prominently including the statement from the approved product labeling, 'OxyContin is

²⁹⁶*Id.* (emphasis added)..

not recommended...for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery).²⁹⁷

167.4. In 2001, FDA repeated the same concerns it had raised in 1995 that OxyContin should not be used in post-operative treatment, for osteoarthritic pain, or for intermittent pain treatment.²⁹⁸

167.5. In addition, on January 17, 2003, FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) issued a warning letter to Purdue regarding off-label promotion for a broader range of patients than indicated:

Your advertisements suggest that OxyContin can be used in a much broader range of pain patients than has been proven to be safe and effective. This is even more problematic from a public health perspective given the serious safety risks associated with the drug and the serious deficiencies in the safety information presented in your advertisements.

The only indication information presented in the body of the advertisements (indeed, the only information from the boxed warning included at all as part of the body of these advertisements) is the partial language from the Indications and Usage section of the PI, "For moderate to severe pain when a continuous, around-the-clock analgesic is needed

²⁹⁷ PURCHI-000622957 at 12.

²⁹⁸ PURCHI-000679976 at 4. FDA noted that OxyContin's indication as provided in the label was "broad and may not adequately reflect the intended population":

She initiated a discussion regarding the drug's intended indication by asking who the proper population is for this type of drug product. The indication of "moderate to severe pain for patients who need to be on opiates for more than a few days" is broad and may not adequately reflect the intended population. The label should clearly state that this drug product should only be used in patients who require opiates for an extended period of time, that it should not be utilized for first-time treatment of pain, and that it is not for intermittent use. She further stated that a black box warning for overdose, abuse and death may be appropriate. Dr. McCormick commented on the studies in the clinical trial section of the label. There are equivalence and open-label studies that are conducted in artificial settings. The arthritis study enrolled patients on non-steroidal and anti-inflammatory agents or IR opiates, for whom OxyContin may not have been the next logical step in pain management. Furthermore, post-operative and ambulatory surgery settings may not be appropriate uses for OxyContin. Dr. Jenkins summarized by saying that the label will need a major overhaul.

Id.

for an extended period of time,” which you present by itself at the top of these advertisements ... These presentations are insufficient to give appropriate context and balance to your claims broadly promoting the use of this drug for pain relief ... Therefore your advertisements fail to adequately communicate the actual indication for OxyContin and suggest its use for pain relief in a much broader range of patients than indicated.

In addition, your advertisements fail to present in the body of the advertisements the other important limitations on the indicated use of OxyContin as noted above... The body of the advertisements, however, fails to present the important limitations on the use of OxyContin restricting it to certain hospitalized patients, as described in the OxyContin Pl... You fail to present in the body of your advertisements any of these important limitations, thus suggesting the use of OxyContin in inappropriate patients.²⁹⁹

168. Before and after FDA’s comments regarding off-label use, Purdue instructed its sales force to “aggressively position OxyContin for use in osteoarthritis, low back pain, post neuropathic neuralgia and post-surgical applications, where appropriate.”³⁰⁰

169. According to sales call notes maintained by Purdue, the sales force promoted and encouraged the use of OxyContin for the treatment osteoarthritis and post-operative pain among other off-label indications, such as for milder pain, short term pain, for “all pain,”³⁰¹ lower back pain, headaches and sprains, which are widely regarded as inappropriate for treatment by a strong opioid product like OxyContin:

²⁹⁹ PKY181392830 at 5-6. Purdue disagreed with FDA’s characterization, stating “[t]he ads do not recommend usage of OxyContin beyond the FDA-approved label indication.” SHC-000008196 at 2. However, Purdue’s internal call notes indicate that its sales force continued to promote for off-label uses. *See* PPLP004032436, PKY182144233, PKY182139597, PKY182145546, PKY182140361, PKY182141419, PKY181917492, PKY181917494, PKY181917498, PPLPMDL0030008507, PPLPMDL0030011819, PKY182156626, PPLPMDL0020000002.

³⁰⁰ SHC-000008166. Further, in an internal Purdue document listing “OXYCONTIN SELLING POINTS,” one selling point was that OxyContin is “[n]ot contraindicated for the treatment of acute and post-op pain,” suggesting that OxyContin can in fact be used safely in those situations. SHC-000008153 at 2

³⁰¹ *See* PPLP004032436 at 64.

169.1. May 23, 1997 (Kentucky) - “NT: USE APS BOOK TO SHOW THAT
OXY APPROPRIATE FOR MILD PAIN THROUGH SEVERE PAIN.”³⁰²

169.2. September 10, 1997 (Ohio) - “**DID COME UP WITH OA AND BACK
PAIN PT FOR USE**, WENT OVR DIF FROM VIC, AND DEFINED CHRONIC USE,
SD WILL USE, FINALLY SD OK TO OXY”³⁰³

169.3. February 9, 1998 (Ohio) - “**LOOKED AT BACK PAIN AGAIN, SD I
NEED NOT WORRY HE USES AS MUCH OXY AS HE CAN**, BUT THEN
AGREED PROBABLY SOME PTCOULD GET MORE RELIEF FROM OXY VS
MAJOR NSAID USE, SD WILL TAKE A LOOK AT THESE PT WHENCOME IN”³⁰⁴

169.4. April 24, 1998 (Ohio) - “**OXY FOR ALL PTS POST OP**/FILE
CARD/POINTED OUT AGAIN HOW TO DOSE/TITRATE/BENEFITS HUGE OVER
SHORT ACT DRUGS/Q12 HR DOSE, NO TYLENOL/LESS ABUSE POTENTIAL.”³⁰⁵

169.5. September 17, 1998 (Ohio) - “FILE WITH BACK PROFILE AND **HOW
THE PI SUPPORTS THE USE STUDY OA, LOW BACK AND POST OP**, LESS
ABUSE POTENTIAL TOO”³⁰⁶

169.6. August 22, 2000 (Ohio) - “TRYING NEW APPROACH TO MD **WILL
SUPPLY WITH MANY MANY STUDIES RE: USES OF OXY IN MANY
DIFFERENT WAYS (I.E. ASYMETRIC IN OSTEOARTHRITIS) TO TRY TO
INCREASE USAGE OF OXY** -THOUGHT BEHIND THIS IF MD THINKS THAT IT

³⁰² PPLP004032436 at 21 (emphasis added).

³⁰³ PKY182144233 (emphasis added).

³⁰⁴ PKY182145546 (emphasis added).

³⁰⁵ PKY182140361 (emphasis added).

³⁰⁶ PKY182141419 (emphasis added).

IS HIS DECISION TO CHANGE HE IS MORE LIKELY TO FOLLOW THROUGH
DECISION; CONTINUE TO SUPPLY HIM WITH INFO RE: OXY AND NEW 160
MG”³⁰⁷

169.7. December 12, 2000 (Ohio) - “**OXY IN OSTEOARTHRITIS STUDY
BY CALDWELL HANDED TO MD** ALONG WITH OXY IR FILE”³⁰⁸

169.8. August 27, 2008 (Ohio) – “He gained information from the physician
about the type of disease states he most likely treats. Dr. said cancer and back pain. **He
asked the physician to prescribe OxyContin instead of short-acting opioid.**”³⁰⁹

169.9. October 27, 2008 (Ohio) – “This was a good call. Dr. started off by
saying he tries not to prescribe OxyContin. **Tom asked probed the Dr. for his
hydrocodone use and pointed out the benefits of low dose OxyContin instead of
hydrocodone/APAP for his low back pain patients.** Dr. said this is what he sees most
of. Tom got the physician to commit to using the 10mg and the benefit the physician saw
was no APAP.”³¹⁰

169.10. February 11, 2010 (Ohio) – “**Nice job getting him to think about
conditions in which he would initiate OxyContin (arthritis, and documented low
back pain).** You had a chance to update him with the Medicaid changes.”³¹¹

170. In my opinion, Purdue promoted OxyContin for indications that were broader
than supported by substantial evidence and for which safety and efficacy were not established.

³⁰⁷ PPLPMDL0030008285 (emphasis added).

³⁰⁸ PPLPMDL0030008285 (emphasis added).

³⁰⁹ PPLPMDL0020000002 (emphasis added).

³¹⁰ PPLPMDL0020000002 (emphasis added).

³¹¹ PPLPMDL0020000002 (emphasis added).

D. Despite Ongoing and Increasing Evidence of OxyContin Abuse, Purdue Failed to Take Reasonable Steps to Correct its Prior Misleading Statements Regarding the Safety of OxyContin and Opioids in General

1. Purdue's Promotion and Sales of OxyContin Increased as Reports of Abuse Grew

171. In the first five years of Purdue's promotion of OxyContin, Purdue increased its marketing expenditures by over 1,300% with sales increasing from less than \$50 million in 1996 to over \$1.08 billion by 2000.³¹² As Purdue acknowledged in 2001, its promotional activities "contributed to a paradigm shift,"³¹³ which expanded the use of opioids in treating pain.³¹⁴

172. As prescriptions and sales of OxyContin increased, Purdue acknowledged that it was anticipating increased reports of abuse and addiction. In an email exchange that began in July 1999, Purdue employees discussed a nurse who was planning to publish a clinical report that highlights OxyContin as a drug of abuse. Robert Reder responded on August 1, 1999 that "this type of report is one which we had been anticipating as the use of OxyContin grow... We have had reports of abuse of OxyContin both through our spontaneous reporting system and through the internet watch set up by Mark [Alfonso]."³¹⁵

³¹² Compare 1998 Budget Plan OxyContin, at PP00123 at 42 with 2002 OxyContin Budget Plan, SHC-000001228 at 58.

³¹³ PDD1503491667 at 1; see also PPLP003409951, PPLP003541889, PPLP004001344.

³¹⁴ In Purdue meeting minutes from an April 23, 2001 meeting between Purdue and the FDA, Purdue agreed that there had been a "shift in prescribing patterns" from malignant to non-malignant pain conditions, including a ten-fold increase in OxyContin prescriptions as compared to extended-release morphine:

It was noted, from 1995 to present there had been a shift in prescribing patterns out of oncology specialties into family practitioners and, when looking by indication, mentions of neoplasm were decreasing and musculoskeletal disease were increasing. Musculoskeletal disease included such terms as lumbago, myalgia and other back pain related terms. Dr. Pollock compared the number of mentions in IMS of OxyContin to MS Contin and noticed that while MS Contin prescribing had remained relatively constant, OxyContin had increased 10 fold. The Agency implied that this was a trend they were concerned with. Mr. Friedman noted that these observations were consistent with our understanding of the data we have seen.

PURCHI-000675080 at 2.

³¹⁵ PKY180233315 at p. 1.

173. In as early as 1997, Purdue's sales force documented reports of addiction and abuse from OxyContin with reports increasing over time,³¹⁶ and by September 29, 2000, Purdue executives had been notified of "abuse of epidemic proportions" as detailed in an email from an internist in Virginia, Dr. Art Van Zee.³¹⁷ In his response to Dr. Van Zee, Purdue's Medical Director, Dr. Haddox, noted to his colleagues that he had not committed to any particular course of action: "I have responded to this email, as well as talking to him personally. I indicated that we were seriously considering his concerns, without committing to any specific course of action."³¹⁸

³¹⁶ See Schedule 11.

³¹⁷ Email from Van Zee to Haddox, Sept. 27, 2000, PKY180296112 at 2 in which Dr. Van Zee stated:

We are seeing oxycontin abuse of epidemic proportions in southwest Virginia. As a primary care general internist in Lee County, Virginia for the last 24 years I have been seeing a very small number of narcotic dependent patients (eg. 1-3 patients per year) in an otherwise busy general internal medicine practice. This started to change about 1-2 years ago when we started seeing increasing numbers of patients that had been abusing oxycontin and had become addicted. The oxycontin is being snorted or IV injected. Most addicts are young, late teen years to their thirties, both men and women. All medical providers in the area are seeing frequently overdoses (some fatal), abscesses, and infections, Hepatitis C, and occasional bacterial endocarditis related to intravenous drug abuse. The expected wave of more Hepatitis C and HIV in the population is sure to follow. The medical, personal, and social costs are extra-ordinary in the poor rural area with few resources to deal with the problems we are facing. There has been an enormous rate of increase in the crime rate which is drug related. In a nearby Tazewell County, the Commonwealth Attorney Dennis Lee has noted that 70% of serious crimes in Tazewell County are now drug related crimes. Our Commonwealth Attorney in Lee County has estimated to me that about "90 percent" of the serious crimes here are drug related. Not a week goes by that I'm not talking with parents about their young adult children that are losing their jobs, spouses, children, and homes to this addiction. Equally frightening to me is that-on a recent county-wide survey in the Lee County School System, 10% of our 7th graders and 20% of our 12th graders have used oxycontin.

Dr. Van Zee urged Purdue to make changes to its marketing:

I think that the whole marketing/advertising approach for Oxycontin needs to be discarded. I think you can understand that the giving of gifts like a beech hat with "Oxycontin" on it, or a CD "Swing is Alive" "Swing in the right direction with Oxycontin"--in light of the medical/personal/social/societal problems related to Oxycontin is way beyond the bounds of distasteful.

Id. In response, Purdue's Dr. Udell agreed, stating "[a]s you know, I agree with Van Zee's criticism of this type of promotional materials." *Id.* at 1.

³¹⁸ PDD8801179978 at 1.

174. In addition, Purdue took steps to minimize negative attention regarding the abuse of OxyContin by focusing on the under-treatment of pain.

174.1. For instance, beginning in 1999, Purdue used public relations firms to monitor local and national news media, state and federal legislatures, advocacy groups, research programs, etc. for “issues/topics in the pain management area that could potentially pose a threat to Purdue Pharma or its products.”³¹⁹

174.2. These firms provided crisis management to Purdue for multiple purposes, including counteracting negative media attention related to the abuse and addiction of OxyContin by “getting information on the patient’s side of the story to reporters.”³²⁰

175. Purdue’s Marketing Department also worked to publish stories that “focus[ed] more on telling the pain management story”³²¹ with Purdue’s Dr. Richard Sackler remarking that “we will have to mobilize the millions that have serious pain and need our product” in the face of negative media attention.³²²

2. FDA Advised Purdue that it Needed to Correct Misinformation Regarding Opioids through a Risk Management Plan and Limit the Expanded Use of Opioids

176. Following increasing reports of abuse, addiction, and diversion,³²³ FDA identified the need for an OxyContin risk management plan in 2001,³²⁴ requesting that Purdue develop

³¹⁹ PKY183037000; *see also* PPLPC045000005939.

³²⁰ PPLPC045000005939; *see also* PPLPC029000036245.

³²¹ PDD1706196246.

³²² PDD8801133516; *see also* PDD1501720041.

³²³ On April 23, 2001, a meeting was held among representatives of Purdue and FDA. FDA’s “Dr. McCormick made opening comments. She stated that the Agency is taking the recent upsurge of prescription drug abuse, and specifically, OxyContin abuse and diversion, very seriously.” PURCHI-000679976 at 3. Citing IMS data, FDA identified one source of the problem being the change in prescribers and patient population, stating that “there has been a shift in primary prescriber-type for OxyContin from 1995 to 2000 from oncologist to family practitioners. The primary indication for which OxyContin is prescribed has also shifted from neoplastic to musculoskeletal disease.” *Id.* The FDA further identified OxyContin’s indication of ‘moderate to severe pain for patients who needs

such a program to include Purdue's advertising of OxyContin.³²⁵ FDA's Dr. Cynthia McCormick stated that she "considers the advertising [of OxyContin] as part of an overall Risk Management Program (RMP) that she sees occurring in two parts":³²⁶

176.1. The first part enunciated by FDA was with respect to prevention, calling for "[c]learer labeling which displays the risk and critical safety messages in a box warning, strengthened warnings about the abuse potential of the product and clarity about the appropriate indication for the product;" "issuance of a Dear Healthcare Provider Letter to alert practicing physicians to the changes in the label;" "retraining of Drug Detail Staff to the key messages of the RMP and the new label;" and "outreach education programs to bring the OxyContin safety message to communities (pharmacies and health care providers) that would be prescribing the product, through outreach educational programs, speakers bureau, CME opportunities and other mechanisms."³²⁷

176.2. The second part to this plan, identified by FDA was "Surveillance, Monitoring and Feedback." Specifically, the FDA stated that "the purpose of surveillance and monitoring is to assess the effectiveness of the prevention and educational part of the

to be on opiates for more than a few days' as being "broad and may not adequately reflect the intended population. The FDA stated that "the label should clearly state that this drug product should only be used in patients who require opiates for an extended period of time, that it should not be utilized for first-time treatment of pain, and that it is not for intermittent use" and that "post-operative and ambulatory surgery settings may not be appropriate uses for OxyContin." *Id.* at 4.

³²⁴ PURCHI-000679976 at 9. Specifically, FDA's Dr. Abrams "suggested an educational campaign to both consumers and practitioners and a national sampling and survey of physicians, inquiring about their perception of the sales representative message and their understanding of the drug and its appropriate uses." *Id.* at 6. FDA's Dr. McCormick "stressed the need for a prospective monitoring program that includes a risk management plan with measurable outcomes." *Id.* at 9.

³²⁵ *Id.*; PURCHI-000551125 at 3.

³²⁶ PURCHI-000551125 at 3.

³²⁷ *Id.*; PURCHI-000551125 at 4.

RMP in curtailing abuse and diversion and to trigger intervention when problems are discovered.”³²⁸

177. On August 3, 2001, Purdue submitted to FDA a proposed Risk Management Program (“RiskMap”) for OxyContin.

177.1. According to Purdue, “[t]he primary goals of this risk management plan are prevention through appropriate labeling and promotion of OxyContin Tablets, and appropriate interventions when significant abuse has occurred or significant risk for abuse has been identified.”³²⁹

177.2. As part of the RiskMAP, Purdue outlined several key messages to be communicated to healthcare providers: “OxyContin is NOT intended for use as a pain analgesic;” “OxyContin is not indicated for pain in the immediate postoperative period (for the first 12 to 24 hours following surgery), or if the pain is mild or is not expected to persist for an extended period of time;” and “OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.”³³⁰

177.3. The RiskMAP also identified how Purdue would disseminate those messages to healthcare providers, including Dear Doctor letters; accredited physician, nursing, and pharmacist continuing education programs; symposia at national/regional organization/society meetings; seminars; monographs; journal supplement; and promotional activities.

3. Despite FDA’s Warnings Regarding the Impact of Misinformation Concerning Opioids, Purdue Failed to Take Reasonable Steps to

³²⁸ *Id.*; PURCHI-000551125 at 5.

³²⁹ PDD8013007919 at 8.

³³⁰ PDD8013007919 at 9-10.

Correct its Misleading Statements and Continued to Expand the Opioid Market

178. Purdue submitted its proposed RiskMAP on August 3, 2001,³³¹ and contrary to the stated goal of this RiskMAP program, many of Purdue’s communications with healthcare provider encouraged the use of OxyContin in manners inconsistent with the approved drug label and the spirit of the risk minimization plan requested by FDA.

178.1. For example, in a pamphlet for doctors, Providing Relief, Preventing Abuse: A Reference Guide to Controlled Substance Prescribing Practices, Purdue told healthcare professionals that addiction “is not caused by drugs.” Instead, Purdue told doctors that addiction only occurs when the wrong patients get drugs and abuses them: “it is triggered in a susceptible individual by exposure to drugs, most commonly through abuse.”³³²

178.2. Another Purdue publication, the Resource Guide for People with Pain, falsely assured patients and healthcare professionals that opioids are not addictive: “Many people living with pain and even some healthcare providers believe that opioid medications are addictive. The truth is that when properly prescribed by a healthcare professional and taken as directed, these medications give relief—not a ‘high.’”³³³

178.3. In addition, Purdue distributed materials published by pain advocacy organizations supported by Purdue that contained false and misleading statements regarding the safety of opioids. For example, Purdue distributed 195,000 copies of guidelines published by the Purdue-funded Federation of State Medical Boards, which included the following misleading statement: “Pseudoaddiction: Pattern of drug-seeking

³³¹ PDD8013007919.

³³² PDD8013350426 at 12.

³³³ PPLP003325237 at 14.

behavior of pain patients who are receiving inadequate pain management that can be mistaken for addiction.”

178.4. Purdue also distributed Exit Wounds: A Survival Guide to Pain Management for Returning Veterans and Their Families misleadingly claimed: “Long experience with opioids shows that people who are not predisposed to addiction are unlikely to become addicted to opioid pain medications.”³³⁴

179. On October 3, 2008, FDA required Purdue to develop Risk Evaluation and Mitigation Strategies (REMS) for OxyContin, finding that “FDA has determined that OxyContin is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients’ decision to use, or continue to use OxyContin.”³³⁵

180. Despite the recognized “serious risks” with OxyContin, Purdue expanded its promotion of OxyContin.³³⁶

³³⁴ SFC00005694 at 107.

³³⁵ PDD8901580306 at 2. Purdue’s REMS for OxyContin identified two primary goals: “To inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction of OxyContin,” and “to inform patients and healthcare professionals about the safe use of OxyContin.” Risk Evaluation & Mitigation Strategy for OxyContin, PPLPC016000016240 at 2, April 1, 2010. To accomplish these goals, Purdue stated it would provide focused education and training to healthcare providers regarding the potential risk of addiction and abuse with OxyContin. *Id.* at 4.

³³⁶ Purdue introduced an abuse-deterrent formulation of OxyContin in 2010, and obtained labeling in 2013 that “OxyContin is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse.” https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf. This did not prevent people from abusing OxyContin orally, *see* PPLP003399733, or from seeking out other drugs to abuse, *see* Evans, William N., Ethan MJ Lieber, and Patrick Power. “How the reformulation of OxyContin ignited the heroin epidemic.” *Review of Economics and Statistics* 101.1 (2019): 1-15 (finding that “each prevented opioid death was replaced with a heroin death”). Purdue stated in 2009, “we understand that introduction of this reformulation may lead to abusers shifting to other opioids.” PDD8901592911 at 6. Furthermore, according to Purdue research from 2015, 82.7% of abusers initiated abuse by taking the drug orally, and by time of treatment admission, 54% of patients admitted to treatment abused the drug this way at least some of the time. PPLP003399733 at 34-35. Notwithstanding, Purdue’s 2014 research found that “majority [of prescribers] consider [ADF] an advantage in the treatment of chronic pain and/or say it has a favorable impact on their perception of opioids.” PPLPC019000902762 at 11.

180.1. In an October 2011 presentation, Purdue instructed its sales force to “extend average treatment duration in appropriate patients” in order to attain their sales target of \$3.9 billion for OxyContin. This instruction was identified as a “strategic imperative” for the company despite growing evidence linking duration of use and abuse of opioids.³³⁷

180.2. In addition, Purdue created a September 13, 2013 presentation that focused on “OxyContin growth opportunities.”³³⁸

180.3. In a July 11, 2014 presentation, Purdue’s Marketing department identified that its sales objective was to “[a]chieve OxyContin Tablet sales of \$1.98 billion” with a marketing program driven by its sales representatives.³³⁹

181. In my opinion, Purdue failed to take reasonable steps to correct its misleading statements and continued to expand the opioid market.

182. As discussed above, Purdue's marketing of OxyContin changed the manner in which opioids were prescribed by healthcare providers. Following Purdue, other manufacturers of opioids adopted to varying degrees marketing strategies and messages that were similar to those employed by Purdue, while also seeking to distinguish their products from Purdue’s OxyContin, and thereby contributed to the change in the practice of medicine and the opioid abuse epidemic.

183. These marketing strategies and messages included the following:

- The risk of addiction with opioids is low or rare
- That one opioid has lower abuse potential or is safer than other opioids
- Minimization of the risk of abuse associated with higher doses of opioids

³³⁷ PPLPC02000385142 at Slide 49.

³³⁸ PPLP004001344.

³³⁹ PPLP003541889 at 13, 44.

- Promotion of the unsubstantiated concept of "pseudoaddiction"
- Promotion of opioids for uses beyond their approved indications and without substantial evidence
- Overstatement of the benefit of opioids with respect to quality of life or functionality
- Misleading claims regarding the abuse-deterrent properties of opioids

VI. ENDO

A. Overview

184. Between 1997 and 2018 Endo promoted or sold various opioid products including Percocet and Opana extended release (ER) and Opana ER reformulated.³⁴⁰

185. Like Purdue and other opioid manufacturers, Endo supported efforts to expand the use of opioids by changing the way healthcare providers view and treat pain.

186. As set forth below, through its support of pain advocacy organizations and development of branded and unbranded promotion, Endo contributed to the expansion of the pain treatment market by promoting pain as an often under-treated condition requiring the use of potent opioid products. In doing so, Endo minimized the risks associated with opioids and misleadingly suggested to healthcare providers that its branded products, Percocet and Opana ER, could be used with minimal risk of abuse and addiction and for uses that had not been shown to be safe and effective by substantial evidence. In parallel with its unbranded promotion, Endo promoted Percocet, Opana ER and Opana ER reformulated in a manner that overstated their benefits and understated their risks—again, telling healthcare providers that these products could be used with minimal risk of abuse and addiction.

³⁴⁰ Other products marketed or sold by Endo include Percodan, Endocet (generic Percocet), Endodan (generic Percodan), generic MS Contin, and generic Oxycontin extended release. ENDO-OPIOID-MDL-02228542 at 10; *see also* ENDO-OPIOID_MDL-04919462.

B. Percocet

187. Percocet is an immediate release combination tablet of acetaminophen and oxycodone, which is a full opioid agonist with relative selectivity for the mu-opioid receptor.³⁴¹

188. Percocet was approved for sale in the United States in 1976.³⁴² Between 1976 and 1999, Percocet was available in 5mg strength only and was marketed by DuPont Merck.³⁴³

189. In 1997, Endo acquired a number of drugs, including Percocet, in a selective buyout of DuPont Merck.³⁴⁴

190. Percocet is Endo's second largest selling opioid to date with over \$1.7 billion revenue.³⁴⁵

1. Endo's Marketing Strategy for Percocet

191. Although DuPont's exclusivity on Percocet had expired by the time Endo purchased the drug, according to Endo's Business Plan and Marketing Strategy for Percocet, Endo planned to obtain approval for higher dosages of the drug, which would allow it to market those dosage strengths during a period of exclusivity and "[o]pportunistically capture share from OxyContin in [the] chronic market."³⁴⁶

192. As described in an April 26, 2002 Endo Quarterly Business Review, a key strategy for Percocet was "[c]onvert[ing] current 5/325mg writers to new Percocet 7.5/325 and 10/325."³⁴⁷ This strategy supported Endo's larger plan of "[e]xpanding and [a]ccelerating usage

³⁴¹ March 2017 Percocet Label.

³⁴² <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=085106>.

³⁴³ ENDO-CHI_LIT-00543478 at 5.

³⁴⁴ See <http://www.endo.com/about-us/history> (last visited Mar. 2, 2019).

³⁴⁵ *Id.*

³⁴⁶ ENDO_DATA-OPIOID_MDL-00000001-0019.

³⁴⁷ ENDO-04908522 at 171.

of Percocet 7.5/325 and 10/325 into the overall oxycodone market during period of exclusivity.”³⁴⁸

2. FDA Approval of Additional Percocet Tablet Strengths

193. On July 26, 1999, Endo obtained approval for Percocet strengths of 7.5/500mg and 10/650mg.³⁴⁹ When Endo’s exclusive right to sell these Percocet strengths expired, Endo sought approval of new Percocet tablets in the 7.5/325 and 10/325 strengths.³⁵⁰ Endo obtained approval of these new strengths on November 23, 2001.³⁵¹ These new strengths contained the same amount of oxycodone as the Percocet tablets approved two years earlier but contained less acetaminophen.³⁵²

3. Endo Funded Promotional Activities for Percocet; Those Activities Understated the Risks of the Entire Class of Opioids

(a) Endo Funded Promotional Activities to Market Percocet

194. Endo’s promotional plans for Percocet included using medical “education” to market Percocet.

194.1. In the “1998 Mid-Year Update on Goals & Objectives” for Endo’s Clinical Development and Education division, Endo’s medical “education” efforts included promotional activities: “[w]orking with sales and marketing teams to successfully execute . . . the Perco variants”³⁵³ and “accelerat[ing] the expansion of

³⁴⁸ ENDO-OPIOID_MDL-04136658 at 7.

³⁴⁹ ENDO-OPIOID_MDL-05396425 at 1. On July 2, 1999, Endo obtained approval for 5/325 mg and 2.5/325mg strengths of Percocet. ENDO-OPIOID_MDL-03453422 at 1. Endo re-launched Percocet 2.5/325 mg in February 2004. *See* ENDO-OPIOID_MDL-03265858 at 2.

³⁵⁰ *See* ENDO-OPIOID_MDL-03388210 at 18 (“[c]onvert current 7.5/500, 10/650 and 5/325 users to new strengths”).

³⁵¹ ENDO-OPIOID_MDL-03453420 at 1.

³⁵² Endo obtained FDA approval for 2.5mg Percocet tablet strengths on July 2, 1999. *See* ENDO-OPIOID_MDL-03453422 at 1.

³⁵³ Linda Kitlinski Depo. Tr. Ex. 1 (ENDO-OPIOID_MDL-05967764).

Endo's branded pain management market through focused educational and Phase IV initiatives" by "[d]evelop[ing] and leverage[ing] strategic alliances with key regional, national and international professional organizations which impact publications, practices and standards of care. (1-4Q 1998)."³⁵⁴

194.2. Similarly, and aligning with Endo's launch of Percocet in 1999, Endo's "1999 Objectives" for its Clinical Development and Education division included a focus on promoting its newly launched Percocet tablets by "[p]artner[ing] with sales and marketing to identify, prioritize and capitalize on educational opportunities which drive attainment of sales quotas," "[w]ork[ing] with sales and marketing teams to successfully launch Percocet 2.5, Percocet 5mg blue, Percocet 7.5mg, Percocet mg,"³⁵⁵ and "[d]evelop[ing] and/or expand[ing] relationships with national professional organizations related to newly-launched products (e.g. American Pain Society) (1-4Q 1999)."³⁵⁶

194.3. An Endo plan for its Clinical Development and Education division entitled "The Critical Connection for Success in 2000 and Beyond," identified objectives that focused on expanding the use of its products, such as Percocet, including: "[a]ttain/exceed financial objectives for promoted products" and "[e]xpand usage of current products by developing and leveraging strategic relationships/alliances,"³⁵⁷ "[e]xpand awareness & usage of Percos ... through acute pain initiatives,"

³⁵⁴ ENDO-OPIOID_MDL-05967764 at 5.

³⁵⁵ Linda Kitlinski Depo. Tr. Ex. 2 at 1 (ENDO-OPIOID_MDL-03258200)

³⁵⁶ ENDO-OPIOID_MDL-03258200 at 1; *see also* Linda Kitlinski Depo. Tr. 68:1-14, 69:8-73:2. Another objective identified by Endo in 1999 included "[u]tiliz[ing] strategic educational program placement and one-on-one discussions with the pain community at national/regional conferences to increase awareness of Endo's newly-launched products. (1-4Q 1999)." *Id.*

³⁵⁷ Linda Kitlinski Depo. Tr. Ex. 3 at 6 (ENDO-OPIOID_MDL-02344002 at 6).

“[s]upport/develop initiatives that combat opioiphobia” “[u]tilize new JCAHO standards as impetus to establish pain mgmt. as a priority w/PCP’s, RPh’s, Neuros.”³⁵⁸

194.4. A 2003-2007 Endo Business Plan reiterated that Endo’s vision in 2001, the same year it obtained approval to market additional Percocet tablets, was to “Drive” the Practice of Pain Management.”³⁵⁹

195. In addition, Endo developed its own pain advocacy organization, the National Initiatives on Pain Control (NIPC), that it funded to advance medical “education” materials that included misleading claims about pseudoaddiction.

195.1. In 2001, NIPC produced the newsletter, *Pain Management Today*, published by Professional Postgraduate Services for healthcare providers.³⁶⁰ This newsletter included a section titled “Key Terms For Opioid Analgesics,” which defined “Pseudoaddiction” as “behaviors that might seem aberrant, but actually indicate inadequate treatment of pain. The behaviors resolve when the pain medication is increased and appropriate analgesia is obtained.”³⁶¹

195.2. NIPC also produced a continuing medical education (CME) presentation in 2002 titled “Advances in Opioid Analgesia: Maximizing Benefit, Minimizing Harm,” claiming that “[p]seudoaddiction” is “behavior suggestive of addiction caused by

³⁵⁸ ENDO-OPIOID_MDL-02344002 at 12. This plan also identified “Unbudgeted Tactics” such as a “National visiting faculty program”³⁵⁸ described as “[c]ritical to expand base of prescribers & avg. # of scripts written” and noted “[e]ffectiveness of ‘peer-to-peer’ influence well-documented.” *Id.* at 22.

Linda Kitlinski Depo Tr. 75:22-24, 76:1-15; 96:19-97:1 (agreeing that “another strategy of [Clinical Development and Education] in the year 2000 was to use JCAHO as an impetus to establish pain management as a priority with primary care physicians.”)

³⁵⁹ ENDO-OPIOID_MDL-04908487.

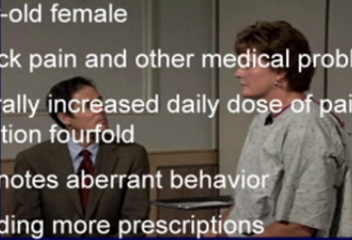
³⁶⁰ **ENDO-OPIOID_MDL-01605952 at 1.**

³⁶¹ **ENDO-OPIOID_MDL-01605952 at 4.**

undertreatment of pain,³⁶² and providing a case history of a hypothetical patient that allegedly showed signs of pseudoaddiction.³⁶³

Case History #3: 46-year-old patient with back pain on multiple medications

- 46-year-old female
- Low back pain and other medical problems
- Unilaterally increased daily dose of pain medication fourfold
- Family notes aberrant behavior
- Demanding more prescriptions
- Is she addicted?



42

195.3. In the speaker notes for this slide, NIPC included the following points:

- As it turns out, this patient's aberrant behaviors are evidence of pseudoaddiction.
- The concept of pseudoaddiction requires elucidation. Some patients may exhibit aberrant behaviors that suggest they have become addicted to their pain medications. The patient may become angry or defensive should any of these demands or behaviors be challenged or thwarted.
- In reality, this patient is not addicted, but is reacting to what might be termed undertreatment of her pain. It is important to realize that not all "addict-like" behavior is an infallible sign of addiction. It might also be a sign of an additional, perhaps as yet undiagnosed, pathology. In this case, the patient's self-medication and demands for more medication are responses to the intense pain caused by metastasizing breast cancer.³⁶⁴

³⁶² KP360_OHIOMDL_000344240 at 41.

³⁶³ KP360_OHIOMDL_000344240 at 48.

³⁶⁴ KP360_OHIOMDL_000344240 at 48.

195.4. In another NIPC CME presentation, the speaker notes encouraged the aggressive use of opioids, stating that “[f]ailure to manage chronic pain aggressively may result in ongoing pain, poor functionality, and patient desocialization.”³⁶⁵

195.5. Similarly, a presentation to the Endo sales force entitled “Barriers to Effective Pain Management,” dated April 23, 2003, explained that “Patient Barriers to Pain Relief” included “Pain medication-related fears” such as “fear of addiction” and after describing addiction stated that “[b]ehaviors suggestive of addiction (e.g., drug seeking behavior) which may occur when patients are not receiving adequate pain relief. If pseudo-addiction, behavior will cease if pain is adequately treated by adjustment in opioid dose.”³⁶⁶

196. Endo also financially supported and was involved with other pain advocacy organizations that put forth “educational” materials and activities that falsely claimed that the risk of opioid addiction had been exaggerated.

196.1. For example, between 1998 and 2003, Endo provided more than \$484,000 in financial support to the American Pain Society (APS).³⁶⁷ As part of those payments to APS, Endo and APS entered into an “agreement” where Endo committed to “\$25,000 (\$10,000 in 1998; \$15,000 in 1999) to the guideline development process” and in exchange Endo’s “CD& E [Clinical Development and Education division] will sit on the

³⁶⁵ KP360_OHIOMDL_000345871 at slide 100 (p.119).

³⁶⁶ ENDO-OPIOID_MDL-02002702 at 12; *see also* ENDO-OPIOID_MDL-02829101 at 62 (slides in an Endo Opioid Analgesics Advanced Sales Training dated April 22, 2003 teach that barriers to appropriate opioid usage in the management of pain include “[m]isunderstanding of common definitions used in pain and addiction medicine” including “[p]seudoaddiction defined as “behaviors similar to addiction,” “[c]aused by undertreatment of pain,” and “[r]esolves upon institution of adequate pain treatment). *Id.* at 7-11.

³⁶⁷ ENDO-OR-CID-00632998 at 7-8. Between 1998 and 2012, Endo made total payments of at least to the APS of \$4,468,253.10.

founding members' guideline committee and provide input into topics for guideline development, as well as suggestions of clinicians for participation in the guideline development process, methods of dissemination/adoptions."³⁶⁸

196.2. Endo also provided more than \$75,000 to the Joint Commission (formerly known as the Joint Commission on Accreditation of Healthcare Organizations or "JCAHO") with the objective of "establish[ing] pain management as a priority with PCPs, RPhs, Neuros."³⁶⁹

196.3. Other organizations that Endo had "develop[ed] and leverage[d] strategic alliances" with by 1998 included:

International Association for the Study of Pain (IASP), American Pain Society (APS), American Academy of Pain Management (AAPM), the American Pain Foundation (APF), the Cochrane Collaboration Group, the American Geriatric Society, and staff at the National Institute of Health/National Institute of Dental Research (NIH/NIDR).³⁷⁰

196.4. By 2004, Endo had "[w]ell-established relationships w/ national/regional societies to support and provide input on major initiatives" with following organizations:

APS, AAPMed, AAPMgmt, IASP, APF, ASPMN, ONS, MASCC, AAFP, ACP, AAN, STFM, ASAM, AOA, ASPAN, AACPI, ASHP, ACPA, NPF, RSDSA, AHS, NHF, ACHE, AAPMR, ACR, AGS, ASRA, AANA, ASA, NSSORA, AAPA, AAHPM, AANP.³⁷¹

³⁶⁸ Linda Kitlinski Depo. Tr. Ex. 4 (ENDO-OPIOID_MDL-06234663). Endo's involvement in developing APS guidelines was reiterated in the "1998 Mid-Year Update on Goals & Objectives" for Endo's Clinical Development and Education division, which stated "through relationships developed with the APS Board of Directors, [Endo] was successful in convincing APS to include clinical education representatives from industry to actively participate on the APS Guideline Development, Dissemination, and Implementation Committee. (APS taking over AHCPR role in pain guideline development.)" ENDO-OPIOID_MDL-05967764 at 5.

³⁶⁹ *Id.* at 12.

³⁷⁰ ENDO-OPIOID_MDL-05967764 at 5. In addition, Endo provided a grant to Professional Postgraduate Services (PPS) that PPS used "to develop and begin implementation of a continuing medical education program on acute and chronic pain conditions." KP360-OHIOMDL_000383569. Endo was permitted to make recommendations for CME physician-speakers. *Id.*

³⁷¹ ENDO-OPIOID_MDL-01139611 at slide 32. APS (American Pain Society); AAPMed (American Academy of Pain Medicine); AAPMgmt (American Academy of Pain Management); IASP (International Association for the

197. The pain organizations supported by Endo published guidelines and other medical “education” materials that contained misleading statements regarding the safety of opioids and were used by Endo.³⁷²

197.1. For example, in 2002, APS published Guidelines for the Management of Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis, 2nd edition,³⁷³ which contained the following misleading statements: “prevalence of addiction among patients with pain who do not have a previously existing substance abuse disorder is low”³⁷⁴ and that “patients who are given doses of opioids that are inadequate to relieve their pain or whose opioid dose is discontinued abruptly or tapered too rapidly may develop characteristics that resemble addiction, which they termed iatrogenic ‘pseudoaddiction.’ Patients are often quite knowledgeable about their medications and the doses that have worked in the past. Requests for these specific medications and doses should not be

Study of Pain); APF (American Pain Foundation); ASPMN (American Society for Pain Management Nursing); ONS (Oncology Nursing Society); MASCC (Multinational Association of Supportive Care in Cancer); AAFP (American Academy of Family Physicians); ACP (American College of Physicians); AAN (American Academy of Neurology); STFM (Society of Teachers of Family Medicine); ASAM (American Society of Addiction Medicine); AOA (American Osteopathic Association); ASPAN (American Society of PeriAnesthesia Nurses); AACPI (American Alliance of Cancer Pain Initiatives); ASHP (American Society of Hospital Pharmacists); ACPA (American Chronic Pain Association); NPF (National Pain Foundation); RSDSA (Reflex Sympathetic Dystrophy Syndrome Association); AHS (American Headache Society); NHF (National Headache Foundation);, ACHE (American College of Healthcare Executives); AAPMR (American Academy of Physical Medicine & Rehabilitation); ACR (American College Of Rheumatology); AGS (American Geriatrics Society); ASRA (American Society of Regional Anesthesia); AANA (American Association of Nurse Anesthetists); ASA (American Society of Anesthesiologists); NSSORA, AAPA (American Academy of Physician Assistants); AAHPM (American Academy of Hospice and Palliative Medicine); AANP (American Academy of Nurse Practitioners).

³⁷² Further detail regarding Endo’s involvement in these pain advocacy organizations is provided below in Section XI.

³⁷³ See PKY181215547; Endo along with Abbott Immunology, Faulding Laboratories, GlaxoSmithKline, Hoechst Foundation, Janssen Pharmaceutica, McNeil Consumer Healthcare, Merck and Co., Inc., Pain Therapeutics, Inc., Pharmacia Corp./Pfizer Inc., Purdue Pharma, and Roxane Laboratories, Inc. contributed to “a common APS Guidelines Program Fund that is used for the support of all APS evidence-based clinical practice guidelines.” *Id.* at 14.

³⁷⁴ *Id.* at 95.

interpreted as necessarily indicating drug-seeking behavior.”³⁷⁵ “As a founding member of the APS guideline committee,” Endo was “entitled to access/distribute copies of the guidelines through [Clinical Development & Education division], and if approved by Endo’s PMRB, through our sales representatives.”³⁷⁶

198. In my opinion, Endo’s marketing activities misleadingly understated the risks of the entire class of opioids.

(b) Endo’s Brand Marketing of Percocet Minimized the Risks of Respiratory Depression and Abuse Associated With Higher Doses of Opioids

199. As discussed in the Purdue section, the greater the dose of opioids, the greater the risk of respiratory depression and abuse.

200. Endo’s marketing strategy for Percocet focused on encouraging the prescription of higher doses and for longer use but did not highlight the increased risks of respiratory depression and abuse.

200.1. For example, a draft 2002 Percocet Business Plan and Marketing Strategy identified key messages for Percocet as including “*Push dose higher. Use longer,*”³⁷⁷ “Continue Percocet use longer in chronic pain patients because lower acetaminophen levels,” and “Increases Percocet daily oxycodone dosage from 60mg to 120mg.”³⁷⁸

200.2. Endo’s 2002 Percocet Business Plan and Marketing Strategy also included the message “Reduction in acetaminophen means less worry about acetaminophen levels

³⁷⁵ *Id.*

³⁷⁶ ENDO-OPIOID_MDL-06234663.

³⁷⁷ ENDO-OPIOID_MDL-03388209 at 7. (Emphasis added)

³⁷⁸ *Id.* at 7; *see also* ENDO-OPIOID_MDL-04908071 at 3 (“Our goal is to convert physicians who prescribe high-strength pain alleviating drugs to the newly launched Percocet 7.5/325 and Percocet 10/325).

and greater dosing flexibility for physicians,” and “Confidence in longer term use means that physicians can reduce the need to switch to other medications.”³⁷⁹

200.3. Similarly, Endo’s 2002 Percocet sales representative detail aid touted the benefits of the increased Percocet strengths: “New Percocet 7.5/325 and 10/325 mg strengths: Effective pain management with less acetaminophen.”³⁸⁰ The detail aid also contains a chart showing the reduced acetaminophen levels in the new Percocet strengths and stated “Confidence in longer-term use with reduced acetaminophen as compared to 7.5/500 and 10/650 mg.”³⁸¹

201. Endo incentivized its sales representatives to promote higher doses to healthcare providers.³⁸²

201.1. For example, a 2002 Endo “Tsunami Launch IC Plan” incentivized the Endo sales force to meet the goal of “pushing higher doses” with “rewards that increased steeply” for “deeper penetration into the *high-strength* [Oxy/APAP] market”—defined as Percocet 7.5/325 and 10/325 and all Oxy/APAP 7.5/500 and 10/650 variants (Percocet, Endocet, and Generic Oxycodone/APAP).³⁸³

201.2. In addition, a presentation to Endo’s sales force titled “Endo State of the Union,” described a “Grand Prix Contest,” measured by “One Metric”—“Percocet TRx increase,” where participating sales representatives and district managers could compete

³⁷⁹ *Id.*

³⁸⁰ ENDO-OPIOID_MDL-04929187 at 3.

³⁸¹ *Id.*

³⁸² See <http://www.endo.com/about-us/history> (last visited Mar. 2, 2019).

³⁸³ (Emphasis added). ENDO-OPIOID_MDL-04908071 at 4. The “high strength Oxy/APAP market segment” was defined to include Percocet 7.5/325 and 10/325, all Oxy/APAP 7.5/500 and 10/650 variants (Percocet, Endocet, and Generic Oxycodone/APAP).

for prizes and the “the opportunity to drive one of six BMWs as their company car starting in mid 2004.”³⁸⁴

202. According to Endo, its promotional efforts resulted in an increase in sales of higher doses of Percocet.

202.1. By 2001, Endo documents characterized the strategy to launch more Percocet tablet strengths “as a success.”³⁸⁵

202.2. According to a Percocet Awareness & Message Tracking Study described in Endo’s 2002 Percocet 1st Quarter Business Review, “the sales message” [in the Percocet 7.5/325 & 10/325 detail aid] worked. “Approximately 90% indicated that [they] have prescribed the new strengths recently”³⁸⁶ and “[m]ore than 60% indicate their prescribing will increase in the future.”³⁸⁷

203. In my opinion, in promoting higher doses of Percocet, Endo misleadingly minimized the risks of respiratory depression and abuse associated with higher doses of opioids.

(c) Endo Overstated the Benefits of Percocet With Respect to Quality of Life

204. Similar to Purdue’s marketing of OxyContin, Endo’s sales training instructed its sales force to make statements based on a single open label study that Percocet improved the quality of life of patients.³⁸⁸ A single open label study does not constitute substantial evidence in which to draw promotional claims.³⁸⁹

³⁸⁴ ENDO-OPIOID_MDL-04911467 at 49; *see also* ENDO-OPIOID_MDL-05589327 at 2.

³⁸⁵ ENDO-OPIOID_MDL-02740383 at 7.

³⁸⁶ ENDO-OPIOID_MDL-049271976 at 16.

³⁸⁷ *Id.*

³⁸⁸ ENDO-OPIOID_MDL-04908364 at 13-14 (“Patients received a statistically significant improvement in all seven QOL parameters and received 39% improvement in overall QOL,” and “Improvement in QOL for patients.”); *see*

205. Statements regarding an improved quality of life associated with Percocet were likewise made to healthcare providers. For example, in a detail aid, Endo stated “New Percocet significantly reduced pain interference with improvement in overall mood, general activity, walking, work, relations, sleep, and enjoyment” and also cited to the open-label clinical trial in support of this claim.³⁹⁰

206. In my opinion, Endo overstated the benefits of Percocet with respect to quality of life.

4. As Reports of Percocet Abuse Grew, Endo’s Promotion and Sales of Percocet Increased

207. After receiving FDA approval to market additional strengths of Percocet in 1999, Endo’s promotional budget of Percocet grew to \$4,256,000 by 2003³⁹¹ with Endo describing itself as the “[c]ompany that Percocet built” and the “company that built Percocet.”³⁹² Sales of Percocet increased from \$40 million to \$214 during this timeframe³⁹³ with a total of 942,959,500 Percocet tablets added to the market by Endo.³⁹⁴

208. Also during this timeframe, evidence of Percocet abuse was rising.

also id. at 15 (“Low Back Study Data . . . Representatives will start using the revised master sales aid after all the district meetings conclude. Week of 4/15.”).

³⁸⁹ In promotion, treatment claims must generally be supported by “substantial evidence” or “two, adequate and well-controlled trials.” An open-label clinical trial is insufficient to satisfy this requirement.

³⁹⁰ ENDO-OPIOID_MDL-04929187 at 7-8, 3.

³⁹¹ ENDO-OPIOID_MDL-04136658 at 11.

³⁹² ENDO-OPIOID_MDL-01139611 at 11.

³⁹³ ENDO-OPIOID_MDL-01139611 at 12.

³⁹⁴ ENDO_DATA-OPIOID_MDL-00000025-41.

208.1. According to an Endo document entitled “Percocet History” “[f]rom 2000-2002, Oxycodone and Hydrocodone accounted for approximately 70% of all narcotic analgesic drug abuse” with Percocet among the top three opioids abused.³⁹⁵

208.2. The same document identified street names for Percocet such as “Percs” and “Percies” and street names for oxycodone products as “Hillbilly Heroine” and “Killer.”³⁹⁶

208.3. According to the National Survey on Drug Use and Health (NSDUH) Report, by 2002 “[a]pproximately 9.7 million individuals age > 12 had used Percocet, Percodan or Tylox for non-medical use at least once.”³⁹⁷

209. In my opinion, as reports of Percocet abuse grew, Endo’s promotion and sales of Percocet increased.

C. Opana ER

210. Opana ER is oxymorphone in an extended release tablet.³⁹⁸ Oxymorphone is an opioid agonist that is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses.³⁹⁹

³⁹⁵ ENDO-CHI_LIT-00543478 at 7. “From 2000-2002, Oxycodone and Hydrocodone accounted for approximately 70% of all narcotic analgesic drug abuse.” *Id.*

³⁹⁶ *Id.* at 9.

³⁹⁷ ENDO-CHI_LIT-00543478 at 7.

³⁹⁸ Opana ER original label (2011). Opana ER is still sold in generic form. In 2010, Endo and Impax Laboratories, Inc. entered into an agreement whereby Impax was authorized to commence selling a generic version of the original formulation of Opana ER on January 1, 2013. Under the terms of this agreement, Impax would pay Endo 28.5% of the sales of its product provided Endo’s sales during the preceding period hit certain benchmarks. EPI001695037 at 12.

³⁹⁹ *Id.*

211. Endo received initial FDA approval to market Opana ER on June 22, 2006 and it has since been withdrawn from the market.⁴⁰⁰ In 2011, Endo received approval to market Opana ER reformulated,⁴⁰¹ which is discussed in the section below.

212. In approving Opana ER, the FDA's Clinical Review stated "[a]s an opioid agonist oxymorphone has similar pharmacological effects as the other drugs of the same class as described in the product labeling for opioid drugs. The major safety issues with the use of opioids are their potential for . . . drug abuse and addiction."⁴⁰²

213. Opana ER and Opana ER reformulated have generated over \$2 billion in combined revenue for Endo.⁴⁰³

⁴⁰⁰ Endo received approval for Opana ER 5, 10, 20 and 40 mg on June 22, 2006 for "the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period time." ENDO-OPIOID_MDL-00298948 at 1. On February 29, 2008, FDA approved 7.5mg, 15mg, and 30mg strengths of Opana ER tablets. These dosages were approved for the same indication.

Opana ER was approved based on enriched enrollment studies. Enriched enrollment is one of several enrichment strategies for clinical trials that can be used according to FDA Guidance to demonstrate efficacy of a drug. *See* FDA Draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products (Dec. 2012)

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf> (accessed Mar. 11, 2019) ("Clinical trials are not designed to demonstrate the effectiveness of a treatment in a random sample of the general population," rather "sponsors use a variety of strategies to select a subset of the general population in which the effect of a drug . . . can more readily be demonstrated."). Enriched enrollment design determines the study population by screening out patients who are non-responsive or suffer serious side effects. *See generally*, FDA Draft Guidance for Industry: Analgesic Indications: Developing Drug and Biological Products at 16 (Feb. 2014),

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384691.pdf> (accessed Mar. 11, 2019) ("2014 Guidance"). First in an open-label titration period, subjects are administered the test drug and titrated to an individually tolerable and effective dose. *Id.* "Only those subjects who can be successfully titrated using prespecified criteria . . . with no intolerable adverse events" proceed and are "randomized to remain on investigational drug or to placebo." *Id.*

The FDA has approved of use of enriched enrollment in clinical trials of opioids. *See e.g., id.* (explaining that it "can be useful for decreasing early dropouts caused by adverse events."). However, enriched enrollment has been criticized. *See generally* ENDO-OPIOID_MDL-04239494 at 2-7.

⁴⁰¹ The approved label for Opana ER reformulated did not include an abuse deterrent labeling claim or a description of the physiochemical properties of the drug. *See* EPI001314350.

⁴⁰² ENO000028976 at 57.

⁴⁰³ ENDO-DATA-OPIOID_MDL-00000008-00000019.

1. Endo's Marketing Strategy for Opana ER

214. According to a 2002 Opana ER Marketing Plan, Endo's "strategic intent" in developing Opana ER was to displace OxyContin and MS CONTIN "as the brand of choice for moderate-severe chronic pain requiring strong opioid analgesia for an extended period of time."⁴⁰⁴

215. During the development of Opana ER, widespread reports of OxyContin abuse and diversion prompted negative attention and investigations by federal and state agencies,⁴⁰⁵ which Endo identified as a point in which to differentiate Opana ER as "[p]hysicians are looking for an alternative to OxyContin because of the media attention and stigma."⁴⁰⁶

215.1. In a 2002 Opana ER Risk Management presentation, Endo noted that it planned to "[c]reate market environment prior to launch that ensures rapid uptake and adoption of [Opana ER]" by "remov[ing] barriers—real and perceived—to prescribers."⁴⁰⁷

215.2. Similarly, in 2002 Opana ER Marketing Plan, Endo stated it would "proactively neutralize opioid abuse issues."⁴⁰⁸

⁴⁰⁴ END00001522 at 11; *see also* ENDO-OPIOID_MDL-04095507 at 21 ("[p]osition Opana as a competitor for oxycodone ER and ER morphine's."). Prior to the approval of Opana ER, the extended release market was dominated by Purdue's OxyContin, which had \$752 million in sales in 2006. *See* PPLPC022001014861.

⁴⁰⁵ *See, e.g.*, ENDO-OPIOID_MDL-04095507 at 5 ("Endo Risk Management Strategy Global Issues": Receptiveness of market to potent, chronic-use opioids has been dampened because of abuse and diversion issues with Purdue's OxyContin, played prominently in the media"); ENDO-OPIOID_MDL-03006242 (OxyContin Abuse and Diversion and Efforts to Address the Problem, General Accounting Office Report, Dec. 2003).

⁴⁰⁶ ENDO-OPIOID_MDL-04095507 at 10; *see also* ENDO-OPIOID_MDL-04095507 at 6 ("Pain Specialists/Policy Makers" "Clearly afraid of abuse and diversion."); END00001522 at 13 ("Concerns over abuse in the spotlight" with "doctors more hesitant to write extended release opioids"); *see also* ENDO-OPIOID_MDL-02002513 at 63; END00000923 at 9; ENDO-CHI_LIT-00550851 at 16; ENDO-CHI_LIT-00552969 at 19.

⁴⁰⁷ *Id.* at 13.

⁴⁰⁸ *Id.* at 14.

216. In addition, to overcome the negative association with opioids, Endo strategized that unbranded marketing, i.e. marketing not directly tied to Opana ER but to opioids in general, would be necessary to rebuild physician comfort with prescribing opioids—and ultimately physician comfort with prescribing Opana ER and would also provide a return on investment for Endo.

216.1. A slide in a March 25, 2002 Opana ER Risk Management Presentation entitled “ROI for [Opana ER] stated: “Potential sales of [Opana ER] depend directly on prescribers’ comfort level with risk of abuse and diversion.”⁴⁰⁹

216.2. In a June 10, 2003 email from Endo’s Senior Director of Clinical Development and Education, Linda Kitlinski, stated that a successful launch of Opana ER needed a CME program by the National Initiative on Pain Control (NIPC), an organization solely supported and funded by Endo,⁴¹⁰ as CMEs are the “only way to credibly talk about opioids in this day and time.” Ms. Kitlinski added that she couldn’t “see how we can successfully launch [Opana ER] without [CME]” concerning opioids.⁴¹¹

216.3. A June 9, 2003 email from Linda Kitlinski to various employees regarding “NIPC Input Needed for Meeting” stated: “Guyz . . . Please hit reply all and let us know 1) your opinion on what the focus . . . of the new module should be. Items to consider in marking this recommendation: a) what will provide the best educational ROI for Endo; b) what the Faculty/Education Council will likely be most receptive to; and c) what will generate best interest/turnout. Given the level of interest and issues surrounding opioids,

⁴⁰⁹ ENDO-OPIOID_MDL-04095507 at 19.

⁴¹⁰ END00152457 at 10.

⁴¹¹ ENDO-OPIOID_MDL-02261843 at 1; *see also* Opana ER 2007-2011 Business Plan, ENDO-CHI_LIT-00545916 at 5 (“Regulatory/Legislative- “More restricted marketing.”)

coupled with our anticipated launch of [Opana ER/IR], I think opioids should be the focus.”⁴¹²

216.4. In this same email, Ms. Kitlinski’s colleague at Endo, Nancy Alvarez, stated: “Opioids should be the focus . . . Nothing new to add except that there is a great need for education as voiced by the last group of advisors . . . They also voiced great concern over the need for pharmacists to receive information as they view them as a major barrier jockeying for position with managed care . . . The return on investment may be to have product available when prescriptions are written.”⁴¹³

216.5. A November 13, 2003 email from Vin Tormo, Clinical Liaison in Clinical Development & Education at Endo regarding “NIPC OPIOID Cinci Program-Fantastic Feedback” stated: “Glad that your recommendation to have the opioid program in Cincinnati paved the way towards, and lessened the fear of appropriately prescribing opioids.”⁴¹⁴

216.6. In the same email Ms. Kitlinski responded on November 16, 2003 and stated: “CONGRATULATIONS on working together to really optimize the value of the NIPC programs for the physicians in your area . . . As we saw with the return on education study conducted this year, the effectiveness of well-planned CME content and well-executed audience recruitment is truly a ‘winning combination.’”⁴¹⁵

216.7. An NIPC invitation invited healthcare providers to “[j]oin your colleagues for an interactive case-based DISCUSSION on **Advances in Opioid Analgesia:**

⁴¹² *Id.* at 2.

⁴¹³ *Id.* at 2.

⁴¹⁴ ENDO-OPIOID_MDL-01928285 at 1.

⁴¹⁵ *Id.*

Maximizing Benefit While Minimizing Risk Dinner Dialogue Series on November 8, 2006” with Grace Forde, MD and Charles Argoff, MD in Roslyn, NY.⁴¹⁶

216.8. In an undated audio recording of an NIPC Dinner Dialogue program entitled “Advances in Opioid Analgesia, Maximizing Benefit While Minimizing Risk,” Dr. Grace Ford told participants “Initial patient assessment. Why assess pain? Well, inadequate assessment is a major, major barrier to treatment. Appropriate decision regarding opioid therapy require[s] a comprehensive assessment. And comprehensive assessment is required by JCAHO. And pain is the Fifth Vital sign. You have to treat patients’ pain adequately. If not you can and you will be sued . . . So we have to be proactive in treating patients’ pain. Assessment is required by opioid treatment guidelines.”⁴¹⁷

217. In addition to rebuilding the opioid brand, Endo formed an Issues Management team prior to the launch of Opana ER to address concerns that “[m]issue/[a]buse risk perception may create negative environment and a PR crisis OxyM and Endo pain franchise”⁴¹⁸

217.1. In a April 27, 2006 email Issues Management Team members forecasted potential harm with Opana ER including: “[d]eath of teen abuser,” “crime reports (pharmacy break-ins, etc) attributed to OxyM seeking,” “Dateline NBC or 60 Minutes type investigation into the approval of another abusable opioid,” “Endo’s Percocet abuse

⁴¹⁶ KP360_OHIOMDL-000003328.

⁴¹⁷ KP360_OHIOMDL_000095691 (17:40-18:15). When asked at her deposition whether Endo paid for a program that threatens to sue doctors for not treating pain adequately, Ms. Kitlinski testified that “Endo cannot control . . . the faculty’s opinions or comments,” but admitted she could not recall ever filing a complaint against Dr. Ford and agreed that Endo continued to support the NIPC until 2012 or 2013. Linda Kitlinski Depo. 219:9-12, 219:16-5, 221:8-9, 12-13, 15-18, 21-24. Ms. Kitlinski also testified that as of 2014, “[t]here were no studies of longer duration than one year” of long-term opioid therapy in patients with chronic pain versus no opioid therapy or nonopioid alternative therapies that evaluated outcomes at one year or longer.” *Id.* at 232:9-15, 18-24.

⁴¹⁸ ENDO-CHI_LIT-00543506 at 3.

history is the subject of investigational reports citing Endo's lack of responsible approach in the past," and "Doctor charged with Rx Fraud in writing [Opana ER]" among other potential crises.⁴¹⁹

217.2. Likewise in early 2006, Endo hired public relations and crisis management company, Waggener Edstrom.⁴²⁰ Waggener Edstrom identified Opana ER weaknesses including (1) product abuse liability is similar to morphine; (2) crushing product or combining it with alcohol can trigger fatal overdose;⁴²¹ and the potential for a "[c]lass-action lawsuit against Endo regarding Opana marketing" and "[r]are, serious adverse event occurs."⁴²²

217.3. In response to these concerns, Endo developed a strategy that included enlisting "Assistance of Key Advocacy Groups," "Prepar[ing] for Positive/Negative Scenarios," Engaging Key Law Enforcement, Federal DEA, U.S. Attorney, State AG's, focusing on OxyContin 'Hot States', and Rapid Response to Critics/Issues,⁴²³ and engaging state regulatory associations and continuing rapid response to media, public constituencies.⁴²⁴

⁴¹⁹ ENDO-OPIOID_MDL-00849563 at 2.

⁴²⁰ ENDO-CHI_LIT-00543384.

⁴²¹ *Id.* at 17.

⁴²² *Id.* at 20.

⁴²³ END00004340 at 3.

⁴²⁴ *Id.* at 3.

2. Endo Promoted Opana ER in a Manner that Understated Its Risks and Overstated Its Benefits.⁴²⁵

(a) Endo Falsely Marketed Opana ER as Having a Lower Abuse Potential and as Safer than Other Opioid Products

218. Oxymorphone, the opioid molecule in Opana ER, has a history of abuse that can be traced back to the 1960s when it was sold by Endo in immediate release form under the trade name Numorphan.⁴²⁶

218.1. In a May 2011 Drug Intelligence Brief, the DEA's Philadelphia Division Intelligence Program described Numporphan as a popular opioid of abuse.

In the early 1970s, oxymorphone in the form of Numorphan instant-release tablets was one of the most sought-after and well-regarded opioids of the class IV drug using community. Popularly known as 'blues' for their blue coloring, the tablets contained very few insoluble ingredients—making them extremely easy to inject—and they were dangerously potent when used intravenously. 'Blues' were also considered to be especially euphoric; better than heroine or morphine."⁴²⁷

218.2. Similarly, the National Institute on Drug Abuse ("NIDA") reported in 1974 that "Numorphan (oxymorphone immediate release) . . . was found to be the object of increased abuse since its appearance in 1966." NIDA cited Numorphan's "rapid onset of action and prolonged duration of effect" as reasons for its popularity.⁴²⁸

219. Endo has likewise acknowledged that Opana ER has an abuse liability similar to other opioids.

⁴²⁵ Kristin Vitanza, Endo's Brand Manager for Opana ER, testified on behalf of Endo that all "Endo reviewed and approved [] promotional materials for . . . Opana ER, both original and reformulated . . ." "were . . . made available for use nationwide in the promotion of Opana ER." Kristin Vitanza Depo Tr. 282:11-283:3.

⁴²⁶ Numorphan was approved for sale in the U.S. in 1959. ENDO-OPIOID-MDL-00156028 at 3.

⁴²⁷ ENDO-OR-CID-00694804 at 2; *see also* WATKINS, TORRINGTON D. & CARL D. CHAMBER, DRUG ABUSE: CURRENT CONCEPTS AND RESEARCH, 307-09 (KEUP, WOLFRAM, ED., 1972) (As of 1972 "abuse of Numorphan appear[ed] to be rather widespread geographically" with "Numorphan . . . identified by its various subcultural names—numorphine, blue morphine, blue morphan, or blues . . .").

⁴²⁸ Endo's predecessor, Endo Laboratories, withdrew Numorphan immediate-release tablets from the market in 1979. ENDO-OPIOID-MDL-00156028 at 3.

219.1. The label for Opana ER warned of Opana ER's abuse liability in a prominent, Blackbox warning reserved for serious or life-threatening risks, noting an abuse liability similar to other opioids:

WARNING: Opana ER contains oxymorphone, which is a morphine-like opioid agonist and a Schedule II controlled substance, *with an abuse liability similar to other opioid analgesics*. Oxymorphone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OPANA ER in situations where the physician or pharmacist is concerned about an increased risk of . . . abuse . . .⁴²⁹

219.2. In addition, Endo's Abuse Liability Assessment for Oxymorphone Extended Release Tablets described the "Risks" of the drug as including that "Oxymorphone is an opioid agonist and a Schedule II controlled substance. It is expected to have an abuse liability similar to other strong opioid analgesics, such as morphine and oxycodone."⁴³⁰

219.3. Endo also included abuse of Opana ER as one of the risks addressed in the Risk Minimization Action Plan ("RiskMAP") for Opana ER,⁴³¹ stating "[t]he goals and objectives for this RiskMAP are to minimize the following liabilities with opioid class of drugs as it pertains to Opana ER . . . Aberrant behavior such as . . . drug abuse . . . [a]mong patients" and "[i]n the community, particularly among your adults." Robert

⁴²⁹ 2006 Opana ER Label (Emphasis in original and added). The current label for Opana ER contains a Blackbox warning with similar language regarding the abuse liability of the drug. *See* 2016 Opana ER Label (ENDO-OPIOID_MDL-00046776 at 4) ("Opana ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death.")

⁴³⁰ ENDO-OPIOID_MDL-00235234 at 36. Abuse of oxymorphone can be traced back to the 1970s. In 1974, the National Institute on Drug Abuse stated in "Drugs and Addict Lifestyles," that "Numorphan (oxymorphone immediate release) . . . was found to be the object of increased abuse since its appearance in 1966. Reasons for its popularity seem to be that it provides rapid onset of action and prolonged duration of effect." FERGUSON, PATRICIA ED., DRUGS AND ADDICT LIFESTYLES, NATIONAL INSTITUTE ON DRUG ABUSE RESEARCH, 237 (1974). In 1979, Endo withdrew Numorphan immediate-release tablets from the market. EPI000130489 at 8.

⁴³¹ EPI000750019 at 8.

Barto Dep. Tr. 1/30/2019 140:7-13, 21-141:7, 142:20-143:2 (“Endo worked with FDA to establish these goals and objectives, and these were the agreed-to goals and objectives with FDA as part of this RiskMAP.”)

219.4. Recently, on January 10, 2019, Endo’s former vice president of sales, Larry Romaine, likewise testified that Opana ER does not have “low abuse potential.”⁴³²

220. Endo witnesses testified that Endo was not permitted to market Opana ER as having less abuse.

220.1. Endo’s former Chief Compliance Officer, Colleen Craven, testified during her deposition, “I agree that Endo was not allowed to say that there was less abuse,” or “less possible diversions of Opana ER for any reason.”⁴³³

220.2. Similarly and in response to the question “you agree that Endo was not allowed to make any of these statements in this sentence about Opana ER: Less abuse, less possible diversion; cannot be crushed; none of the statements were allowed to be made, right?” Ms. Craven testified: “Correct.”⁴³⁴

220.3. Endo’s Vice President of Sales and Regional Business Director, Ronald Jackson similarly testified that it would be “improper” for Endo sales reps “to try to downplay stated risks with respect to a product.”⁴³⁵

221. Despite testimony from Endo’s witnesses that it was not permitted to market Opana ER as having less abuse liability, Endo’s sales force falsely marketed Opana ER as safer than other opioids because of reduced abuse liability.

⁴³² See, e.g., Larry Romaine Depo. Tr. 352:12-14, 16-24.

⁴³³ Collen Craven Dep. Tr. (356:13-357:3, 357:5-7).

⁴³⁴ Craven Dep. Tr. (358:1-6).

⁴³⁵ Ronald Jackson Depo. Tr. 289:9-12.

221.1. Following the launch of Opana ER in June 2006, Endo commissioned market research to identify physician perceptions of Opana ER called Awareness, Trial and Usage (“ATU”) studies.⁴³⁶ These studies confirmed that Endo’s messages that Opana ER had low abuse potential and was safer were being delivered to physicians.

221.2. A June 2007 ATU study of physician recall/perceptions reported that “low abuse potential and safety and tolerability were regarded as the main advantage of Opana ER.”⁴³⁷

221.3. A 2008 ATU study confirmed that one year later physician perceptions remained similar. The study stated that physician awareness of Opana’s “lack of street value” led to “a perception of lower potential for street abuse.”⁴³⁸ The study also reported that physicians who anticipated prescribing increases for Opana ER over the next 6 months” cited “‘low abuse potential’” as one of two major reasons for choosing Opana ER.⁴³⁹

221.4. Market research from 2008 indicated that “PCPs prefer hearing that the agent they select for treatment would be less risky and therefore, easier for them; they reported a sense of calm after reading the ‘simple’ statement.”⁴⁴⁰

221.5. In an Opana ER W2 IVR Vocal Response Listing examining Endo sales representative in-person sales presentations, certain doctors reported that the “main message of the most recent presentation [they] received” for Opana ER included “Less

⁴³⁶ *Id.* at 342:18-343:4.

⁴³⁷ *Id.* at 343:8-12, 343:16-344:2, 5-6.

⁴³⁸ ENDO-CHI_LIT-00547543 at 12.

⁴³⁹ *Id.*

⁴⁴⁰ ENDO-CHI_LIT-00023299 at 38.

euphoria and maybe less addictive potential,” “safe, long acting, *less abuse potential*,” and “The delivery system and *low abuse potential*.”⁴⁴¹

221.6. A December 2008 ATU Final Report stated that Opana ER had “an opportunity to build on one of its most important strengths—low abuse potential.”⁴⁴²

221.7. Endo’s market research from 2008 showed that “Low abuse Potential” was the primary factor influencing physicians’ anticipated increase in use of Opana ER.”⁴⁴³

221.8. Endo sales reps facilitated letters written by doctors to the West Virginia Medicaid Pharmaceutical & Therapeutics Committee, that understated the risk of abuse, stating “Opana ER has a unique delivery system which involves a Matrix, thus allowing it to be given twice a day. The Matrix also allows for the chance of less abuse and possible diversion since it cannot be crushed allowing for injection or nasal administration.”⁴⁴⁴

221.9. In 2009 and 2010, between 15- 21% of physicians surveyed maintained the perception that “advantages of Opana ER” included “low abuse potential.”⁴⁴⁵

221.10. Endo’s Vice President of Sales, Larry Romaine, testified that “Endo could have sent out a Dear Doctor letter to the prescribers it was servicing,” in order to correct the misperception that Opana ER had a low abuse potential and that this

⁴⁴¹ ENDO-CHI_-LIT-00150080 (Emphasis added).

⁴⁴² ENDO-CHI_LIT-00547543 at 17.

⁴⁴³ ENDO-CHI_LIT-00023299 at 59.

⁴⁴⁴ ENDO-OPIOID_MDL-0380727 at 3.

⁴⁴⁵ ENDO-CHI_LIT-00023394 at 55; ENDO-CHI_LIT-00012061 at 37. Six percent of physicians interviewed reported that “[l]ow abuse potential” was the “first thing that comes to mind when [they] think of Opana ER.” *Id.* at 36.

misperception was driving their prescription decisions.⁴⁴⁶ Mr. Romaine could not recall whether such a letter was sent.

222. In my opinion, Endo falsely marketed Opana ER as having a lower abuse potential and as safer than other opioid products.

(b) Endo Minimized the Risk of Addiction Associated with Opana ER and Funded Various Pain Organizations to Likewise Minimize the Risk of Addiction

223. Oxymorphone is known to be addictive, which Endo recognized in seeking approval of Opana ER.

223.1. An article from the New England of Journal of Medicine included in the Opana ER NDA explained: “[t]here can be no doubt, however, that prolonged administration of Numorphan [oxymorphone] represents considerable addiction liability.”⁴⁴⁷

223.2. Addiction risk as it pertains to Opana ER was also one of the risks that Endo told FDA it was addressing through its Risk Minimization Action Plan (“Risk Map”) for Opana ER.⁴⁴⁸

224. Nonetheless, Endo minimized the addiction potential of oxymorphone discussed above by telling healthcare providers and patients that the risk of addiction with Opana ER and opioids was low.

⁴⁴⁶ Larry Romaine Dep. Tr. 360:9-12, 16-21, 360:24-361:14.

⁴⁴⁷ ENDO-OPIOID-MDL-00235351 at 4.

⁴⁴⁸ EPI000750019 at 8 (“The goals and objectives for this RiskMAP are to minimize the following liabilities with opioid class of drugs as it pertains to Opana ER . . . Aberrant behavior such as . . . addiction . . . [a]mong patients” and “[i]n the community, particularly among your adults.”); Robert Barto Dep. Tr. 1/30/2019 140:7-13, 21-141:7, 142:20-143:2 (“Endo worked with FDA to establish these goals and objectives, and these were the agreed-to goals and objectives with FDA as part of this RiskMAP.”)

224.1. A 2009 Opana ER “Instant Savings” card and Resource Kit promising patients up to \$300 in savings asked “What is the risk of becoming addicted to a long-acting opioid?” In response, the accompanying information kit stated “[m]ost healthcare providers who treat patients with pain agree that patients treated with prolonged opioid medicines usually do not become addicted.”⁴⁴⁹

224.2. Endo’s website for Opana, www. Opana.com broadcasted the statement “Most doctors who treat patients with pain agree that patients treated with prolonged opioids medicines usually do not become addicted” until at least 2012.⁴⁵⁰

225. Endo also delivered the misleading message that opioids have low addiction potential through pain advocacy organizations and medical societies it funded.⁴⁵¹

225.1. A December 2007 NIPC *Pain Management Today* newsletter told healthcare providers: “[p]atients are also concerned with being looked upon as ‘druggies’ even though risk of addiction in the general population treated with chronic opioid therapy is extremely low. This adds to the psychological issues that often accompany chronic pain conditions.”⁴⁵²

⁴⁴⁹ ENDO-CHI_LIT-00541205 at 7. A 2010 Oxymorphone Franchise Tactical Plan by Chad Simon, Sr. Product Manager, for the OPANA Brand, reported that the Opana Instant Savings Program had a 14% redemption rate in 2009 for a total of 58,227 redemptions in the range of \$21-25 nationally and between 4,000 and 7,000 redemptions in Ohio. ENDO-CHI_LIT-00039111 at 31.

⁴⁵⁰ END00474717 at 23.

⁴⁵¹ According to Endo’s May 2012 response to the Hon. Max Baucus and Hon. Charles E. Greeley, then Chairman and a member of the Senate Finance Committee, between 1997 and 2012, Endo paid millions of dollars to the American Pain Foundation, American Academy of Pain Medicine, American Pain Society, American Geriatrics Society, University of Wisconsin, Beth Israel Medical Center, the Joint Commission on Accreditation, and the Federal State Medical Boards. ENDO-OR-CID-00754369 at 24-32.

⁴⁵² KP360_OHIOMDL_000027041; Ms. Kitlinski testified that it was Endo’s “intent” “that doctors of all backgrounds, of all specialties, in training or in practice for a long time, had exposure to the company’s supported education programs,” including through the NIPC.” Linda Kitlinski Dep. Tr. (1/15/2019) 395:11-19, 395: 22-24, 396:1-7.

225.2. Endo also provided financial assistance to the American Academy of Pain Medicine (“AAPM”) and the American Pain Society (“APS”), and distributed to healthcare providers the 1997 AAPM/APS consensus statement, which downplayed the risk of addiction, stating that “studies indicate that the de novo development of addiction when opioids are used for the relief of pain is low.”⁴⁵³ The Consensus Statement failed to identify any of the “studies” that it claimed “indicate[d] that the de novo development of addiction when opioids are used for the relief of pain is low.”⁴⁵⁴

226. In my opinion, Endo minimized the risk of addiction associated with Opana ER and funded various pain organizations to likewise minimize the risk of addiction.

(c) Endo Falsely Told Healthcare Providers that Patients Exhibiting Signs of Addiction Could be Exhibiting “Pseudoaddiction” and in Need of Additional Opioids to Treat Pain

227. As described in the Purdue section, the concept of pseudoaddiction is not supported by substantial evidence.

228. Despite a lack of substantial evidence for the concept of pseudoaddiction, Endo included the term in its sales training materials for Opana ER.

228.1. A 2006 Endo sales training document entitled “Module 3: Oxymorphone Risk Management Program” contained a list of definitions “of five important but commonly misunderstood terms” including “Pseudoaddiction,” which it defined as a “term used to describe iatrogenic phenomenon in which a patient with undertreated pain

⁴⁵³ ENDO-OPIOID_MDL-00925807. Endo distributed the Consensus Statement including as part of its risk minimization plan for generic oxycontin and Opana ER. EPI000799695 at 14; ENDO-OPIOID_MDL-01500831 at 14.

⁴⁵⁴ The Consensus Statement was prepared by “committee members” and a “consultant,” many of whom were paid speakers for Purdue, e.g., J. David Haddox, *see* PKY180955294, *see* _____, Russell K. Portenoy, MD, *see* PKY180357269.

is perceived by healthcare professionals to exhibit behaviors similar to those seen in addiction but is not truly addicted.”⁴⁵⁵

228.2. The sales training document added: the “physician can differentiate addiction from pseudoaddiction by speaking to the patient about his/her pain and increasing the patient’s opioid dose to increase pain relief. Pseudoaddiction behaviors such as clock watching (counting down the time until the next dose) will resolve when the pain is properly treated.”⁴⁵⁶

229. In addition, pain advocacy and professional medical organizations supported by Endo published “educational” materials that recognized pseudoaddiction as a medical condition despite the lack of substantial evidence.⁴⁵⁷ For example, at a 2009 NIPC CME on Chronic Opioid Therapy: Understanding Risk While Minimizing Analgesia, Dr. Perry Fine, a paid speaker,⁴⁵⁸ discussed a hypothetical patient who although instructed not to change her pain treatment plan without consulting her doctor, increased her short-acting opioid. Dr. Fine told an audience of healthcare providers:

We need to understand the definitions of pseudoaddiction and behaviors that may resemble frank abuse or addictive behaviors which, in fact, may be extinguished by good pain control. It is a very important distinction to make.” “The diagnosis is extraordinarily important since addiction is a primary neurobiological disease that is life threatening and needs to be very carefully managed, where pseudoaddiction may reflect a very different issue.” Dr. Fine concluded “In view of this differential diagnosis, Dr. Jones believes that in fact this may represent a combination of tolerance and pseudoaddiction and behaviors that are motivated by pain rather than drug-seeking, per se.”⁴⁵⁹

⁴⁵⁵ ENDO-CHI_LIT-00053284 at 15.

⁴⁵⁶ *Id.* at 16. The sales training module cited to the “AAPM, 2001” for these statements. *Id.*

⁴⁵⁷ *See* Section XI.

⁴⁵⁸ *See, e.g.*, KP360_OHIOMDL_000037538.

⁴⁵⁹ KP360_OHIOMDL_000121559 at 1, 26.

229.1. Pseudoaddiction was also taught to 3rd and 4th year residents and fellows in Anesthesiology, Neurology, Family Practice, Emergency Medicine and Physical and Rehabilitation Medicine at the APS's Endo-supported "Fundamentals of Pain Management" "intensive two-day course" attended by more than 1,150 residents and fellows.⁴⁶⁰ Specifically, a slide in the 2009 syllabus for the APS's "Fundamentals of Pain Management" stated: "Differential Diagnosis of Aberrant Drug-Taking Attitudes and Behavior" and included "Pseudoaddiction (inadequate analgesia)" as one of five diagnoses along with addiction, chemical copers, other psychiatric diagnosis, and criminal intent."⁴⁶¹

229.2. As late as 2012 NIPC continued to deliver a message of pseudoaddiction to healthcare providers. An NIPC Dinner Dialogue CME entitled Responsible Opioid Prescribing in the Era of REMS,⁴⁶² attended by 486 prescribers from around the country⁴⁶³ including Columbus, Ohio,⁴⁶⁴ presented a clinical case and asked "Although NB had good general pain control with use of his treatment plan, over time, his pain has increased, and he has increased his dosage of medication without permission with no additional benefit. What is the differential diagnosis? 1. Tolerance, 2. Pseudoaddiction, 3. Addiction, 4. Misuse, 5. Abuse, 6. Diversion."⁴⁶⁵

⁴⁶⁰ Linda Kitlinski Deposition, Ex. 41.

⁴⁶¹ ENDO-OPIOID_MDL-05968029 at 38.

⁴⁶² CHI-000929476 at 1.

⁴⁶³ KP360_OHIOMDL_000336756 at 1.

⁴⁶⁴ KP360_OHIOMDL_000336605 at 2.

⁴⁶⁵ ENDO-OR-CID-01252970 at 57; *see also id.* at 58 (pseudoaddiction is defined as "syndrome resulting from undertreatment of pain that is misidentified by the clinician as inappropriate drug-seeking behavior. Behavior ceases when adequate pain relief is provided. Not a diagnosis; rather, a description of a clinical interaction.")

230. In my opinion, Endo falsely told healthcare providers that patients exhibiting signs of addiction could be exhibiting “pseudoaddiction” and in need of additional opioids to treat pain.

(d) Endo’s Promotion of Opana ER Minimized the Risks of Respiratory Depression, Addiction and Abuse Associated With Higher Doses

231. Consistent with Purdue’s minimization of the risks associated with higher doses of opioids in its message that OxyContin had no dose ceiling, Endo told healthcare providers that the dose of Opana ER could be adjusted upward without disclosing the potentially fatal risks of respiratory depression and the increased risk of abuse.

231.1. A 2009 Opana ER “Instant Savings” card and Resource Kit told potential Opana ER patients “[s]ome people taking opioids may need to take a higher dose after a period of time in order to have relief from their pain. This is ‘tolerance’ to opioid medications that doesn’t affect everyone who takes them and does **NOT** mean addiction. (Emphasis in original). If tolerance develops, it does not mean you will ‘run out’ of pain relief. Your healthcare provider can adjust your dose or prescribe another medicine.”⁴⁶⁶

231.2. An Endo sponsored brochure entitled Understanding Your Pain: Taking Oral Opioid Analgesics brochure delivered a similar message regarding opioids. In response to the question, “what should I know about opioids and addiction,” the brochure stated: “If tolerance does occur, it does not mean you will ‘run out of’ pain relief. Your dose can be adjusted or another medicine can be prescribed.”⁴⁶⁷

⁴⁶⁶ *Id.*

⁴⁶⁷ ENDO-CHI_LIT-00237187 at 3.

232. In my opinion, Endo's promotion of Opana ER as having no dose ceiling misleadingly minimized the risks of respiratory depression, addiction and abuse associated with higher doses.

(e) Endo Overstated the Benefits of Opana ER With Respect to Work and Functionality

233. Endo did not have adequate and well controlled clinical studies demonstrating that Opana ER improved functionality.

234. Nevertheless, Endo promoted Opana ER as providing pain relief that increases patients' functionality.

234.1. A "Clinical Case Study" featuring a clinical perspective by Gerald M. Aronoff, MD presented a hypothetical patient overview of "Laurie."⁴⁶⁸ Under "Patient Assessment/Diagnosis," it stated "Laurie is an otherwise healthy middle-aged woman presenting with inadequately controlled chronic back pain despite total daily dose of 120 mg OxyContin plus oxycodone/acetaminophen 5 mg/325 mg PRN for supplemental rescue medication. Patient reports difficulty remaining active because of her chronic pain, resulting in a sense of loneliness and isolation."⁴⁶⁹ The "Treatment Goals and Plan" section of the case study stated "[t]he ultimate goal of therapy will be to obtain an appropriate balance between management of pain and suffering, improving daily function, and minimizing opioid-related adverse actions . . . Help Laurie, who may feel isolated and stranded due to her condition, by developing a comprehensive pain management plan . . . Begin OPANA ER (oxymorphone HCl) Extended-Release tablets,

⁴⁶⁸ ENDO-CHI_LIT-00138534 at 3.

⁴⁶⁹ *Id.*

CII, with INTAC technology plus supplemental rescue therapy with OPANA Immediate Release (IR).⁴⁷⁰

234.2. Endo also used hypothetical patient profiles to tout the functionality benefits of Opana ER. In a 2007 “Bill the Patient” profile used with physicians, Endo presented Bill—a “40 year old male construction worker who needs to work to support his family,” with “moderate to severe low back pain treated with pain medication for several months,” and whose “[p]hysician has determined patient is appropriate for continuous around-the-clock opioid therapy.”⁴⁷¹

234.3. In a 2011 patient profile, Endo presented “Frank,” an “[a]uto mechanic whose job requires him to stand on his feet all day,” and who has “been treated for chronic low back pain for 3 years.” The promotional piece continued “[b]ecause Frank is not experiencing adequate pain relief, his physician has been upwardly titrating his dose to increased side effects . . . Frank needs a different long-acting opioid.”⁴⁷²

235. In my opinion, Endo misleadingly overstated the benefits of Opana ER with respect to work and functionality.

3. Endo’s Risk Minimization Action Plan for Opana ER Contained Elements that Understated the Risk Abuse and Addiction and Misleadingly Claimed that Patients Exhibiting Signs of Addiction Were Likely “Pseudoaddicted”

236. To address the risks posed by Opana ER, prior to approval, on October 4, 2001, FDA informed Endo that a risk management program for the drug would be needed at the time of approval.⁴⁷³

⁴⁷⁰ *Id.* at 4.

⁴⁷¹ ENDO-CHI_LIT-00033952.

⁴⁷² ENDO-CHI_LIT-00099937 at 1.

⁴⁷³ ENDO-OPIOID_MDL-00159347 at 4.

236.1. During an August 6, 2003 teleconference between FDA and Endo representatives, FDA “provide[d] Endo with an outline of the essential elements required in a Risk Management Plan (RMP).”⁴⁷⁴ Endo’s minutes of the teleconference reflect that FDA stated: “In general the Agency believes that a RMP should address 3 elements: (1) “Risk of accidental exposure”; (2) “Improper patient selection-how should a physician be selecting patients;” and (3) “Risk for abuse and misuse-how can we reduce risk for patient and community.”⁴⁷⁵

236.2. Consistent with the above, Endo’s former vice president of regulatory affairs, Robert Barto, testified during his deposition that “[a]n agreed-to risk minimization plan with FDA was necessary in order to secure approval for the product.”⁴⁷⁶

237. Endo’s June 2007 Risk Minimization Action Plan for Opana ER made certain representations to FDA including:

237.1. “Endo has developed and is constantly striving to improve a comprehensive ‘Risk Minimization Action Plan (RiskMap) for [Opana ER], which aims to promote the safe and responsible use of the product while concurrently minimizing abuse, misuse, diversion and other adverse events through appropriate drug labeling, tight controls on distribution, proactive pharmacovigilance, extensive education of healthcare professionals and sales personnel, and funding of clinical meaningful research.”⁴⁷⁷

⁴⁷⁴ ENO000087335 at 1.

⁴⁷⁵ *Id.*

⁴⁷⁶ Robert Barto Dep. Tr. (Jan. 30, 2019) 137:3-5, 7-10.

⁴⁷⁷ ENDO-OPIOID_MDL-00290299 at 7.

237.2. Endo represented that its “goals and objectives for this RiskMap are to minimize the following liabilities with opioids class of drugs as it pertains to [Opana ER/IR]” including:

- “Aberrant behavior such as drug abuse, misuse, and addiction” “[a]mong patients” and “[i]n the community, particularly among young adults,”
- “Unintentional drug overdose”
- “Accidental exposure”
- “Diversion from distribution/manufacturing facilities”
- “Improper patient selection”
- “Fraudulent prescription activity”
- “Inadequate patient education”⁴⁷⁸

238. Endo’s RiskMAP for Opana ER also told FDA that it had developed strategies and tools “to minimize the potential risks that may be associated with [Opana ER/IR]” and further represented that “Endo’s RiskMAP is designed to protect the public and help minimize abuse, misuse, and diversion.”⁴⁷⁹

238.1. These “[s]trateg[ies] and [t]ools” included Product Labeling, Education consisting of “Professional Education Initiatives” such as continuing medical education (“CME”) presented by various educational media such as: National Initiative on Pain Control (“NIPC”) Dinner Dialogue Programs, audioconferences, half-day symposia, newsletters and webcasts, thePainEdu.org website and manual,⁴⁸⁰ the AAPM/APS

⁴⁷⁸ EPI000750019 at 8; Robert Barto Dep. Tr. (1/30/2019) 140:7-13, 21-141:7, 142:20-143:2 (“Endo worked with FDA to establish these goals and objectives, and these were the agreed-to goals and objectives with FDA as part of this RiskMAP.”)

⁴⁷⁹ *Id.* at 8-9.

⁴⁸⁰ According to the Opana ER RiskMAP, *PainEdu* “makes use of case-based learning, roundtable discussions, ‘ask the expert’ modules, downloadable tools such as SOAPP, an electronic download of the Clinical Companion

Consensus Statement on the Use of Opioids for the Treatment of Chronic Pain, and the Pain Action website, among other components.⁴⁸¹

238.2. Bob Barto, Endo's Vice President of Regulatory Affairs, likewise confirmed during deposition testimony that "education" including National Initiative on Pain Control programming, www.PainEdu.org, AAPM/APS, Pain Action, and oversight of the distribution chain were part of the risk minimization plan for Opana ER.⁴⁸²

239. As discussed below, Endo's RiskMap for Opana ER contained elements that understated the risk of abuse and addiction and misleadingly claimed that patients exhibiting signs of addiction were likely "pseudoaddicted."

(a) Elements of the "Professional Education Initiatives" in the Opana ER RiskMap Falsely Told Healthcare Providers that Patients Exhibiting Signs of Addiction Could Be Exhibiting "Pseudoaddiction" and in Need of Additional Opioids to Treat Pain

240. Despite Endo's representation to FDA that its RiskMAP for Opana ER was designed to address the risks of Opana, components of the Professional Education Initiatives in the Opana ER RiskMap taught healthcare providers the concept of pseudoaddiction—the unsubstantiated claim that signs of drug seeking are pseudoaddiction rather than addiction and require more opioids to resolve.⁴⁸³

manual and makes use of varied educational strategies." *Id.* at 16. Endo funded the "development, maintenance and continued enhancement of *PainEdu*." *Id.*

⁴⁸¹ *Id.* at 2.

⁴⁸² Barto Depo Tr. 143:21-144:14; 146:19-22. Mr. Barto suggested that the RiskMAP "didn't work." *See* Barto Depo Tr. 244:20-24 ("If the RiskMap didn't work and communicating to healthcare providers didn't work, then moving to another system might have similar challenges in being effective. I thought maybe a different tact to go directly to the public would be of benefit.")

⁴⁸³ *See* discussion of pseudoaddiction in Purdue section.

240.1. Between October 26, 2006 through December 12, 2006, NIPC hosted a Dinner Dialogues Series entitled “Advances in Opioid Analgesia: Maximizing Benefit While Minimizing Risk” held in cities around the United States. Endo described the program as one that “specifically, address[ed] the responsible prescribing of opioid analgesics.”⁴⁸⁴

240.2. A slide in the presentation entitled “Advances in Opioid Analgesia: Maximizing Benefit While Minimizing Risk” described “Pseudoaddiction” as a “Pattern of drug-seeking behavior of patients with pain receiving inadequate pain management that can be mistaken for addiction” and identified purported signs of pseudoaddiction such as “concerns about availability,” “clock watching,” and unsanctioned dose escalation.” The slide stated that “pseudoaddiction” may “resolve with reestablishment of adequate analgesia or adjustment of analgesic dose/schedule.”⁴⁸⁵

240.3. An NIPC Dinner Dialogue CME entitled Responsible Opioid Prescribing in the Era of REMS,⁴⁸⁶ attended by 486 prescribers from around the country⁴⁸⁷ including Columbus, Ohio,⁴⁸⁸ presented a clinical case and asked “Although NB had good general pain control with use of his treatment plan, over time, his pain has increased, and he has increased his dosage of medication without permission with no additional benefit. What

⁴⁸⁴ EPI000750019 at 11.

⁴⁸⁵ ENDO-CHI-LIT-00544711 at 6.

⁴⁸⁶ CHI-000929476 at 1.

⁴⁸⁷ KP360_OHIOMDL_000336756 at 1.

⁴⁸⁸ KP360_OHIOMDL_000337097.

is the differential diagnosis? 1. Tolerance, 2. Pseudoaddiction, 3. Addiction, 4. Misuse, 5. Abuse, 6. Diversion.”⁴⁸⁹

240.4. An NIPC audioconference series entitled “Advanced in Opioid Analgesia, Maximizing Benefit While Minimizing Risk” presented by Dr. B. Elliott Cole instructed a group of 50 healthcare providers: “pseudoaddiction is . . . clock watching behavior . . . that suggests . . . they’re not getting enough medication and often what fixes their aberrant behavior is a dose increase to the point where they become comfortable.”⁴⁹⁰

240.5. The Pain.edu website and Manual similarly downplayed concerns about addiction by claiming a distinction between pseudoaddiction and addiction. The Manual for Painedu.org under the topic “Prescribing Considerations” stated: “Two major considerations are important when prescribing opioids: the *fear of regulatory and legal scrutiny* and the *fear of addiction*, which can ultimately contribute to the undertreatment of pain. Fears of sanctions by regulatory agencies are largely exaggerated . . . Another fear that leads to the undertreatment of pain with opioids is addiction. It is important that the clinicians understand and be able to convey to the patient and family, the distinction between physical dependence, addiction and pseudoaddiction . . . *Pseudoaddiction* is a term used to describe behavior that appears to be addictive, ‘drug seeking’ behavior but is actually an effort to obtain pain relief by a nonaddicted patient who is not receiving adequate analgesia.”⁴⁹¹

⁴⁸⁹ ENDO-OR-CID-01252970 at 57; *see also id.* at 58 (pseudoaddiction is defined as “syndrome resulting from undertreatment of pain that is misidentified by the clinician as inappropriate drug-seeking behavior. Behavior ceases when adequate pain relief is provided. Not a diagnosis; rather, a description of a clinical interaction.”)

⁴⁹⁰ KP360_OHIOMDL_000017045 (transcribed) (56:35-56:61).

⁴⁹¹ END00051444 at 127-28, 131.

240.6. *A clinical guide to Opioid Analgesia* authored by Russell Portenoy, MD and Perry Fine, MD⁴⁹² under the heading “Pseudoaddiction” stated: “Pseudoaddiction refers to the development of abuselike behaviors that are driven by desperation surrounding unrelieved pain and are eliminated by measures that relieve the pain, such as increase in medication dose.”⁴⁹³

241. In my opinion, the above referenced components of the “Professional Education Initiatives” in the Opana ER Riskmap falsely told healthcare providers that patients exhibiting signs of addiction could be exhibiting “pseudoaddiction” and in need of additional opioids to treat pain.

(b) Elements of the “Professional Education Initiatives” in the Opana ER RiskMap Minimized the Risk of Addiction Associated with Opioids

242. Notwithstanding Endo’s representation to FDA that its RiskMAP for Opana ER was designed to address the risks of Opana, components of the Professional Education Initiatives in the Opana ER RiskMap minimized the risk of addiction associated with opioids and Opana ER.

242.1. The “AAPM/APS ‘Consensus Statement on the Use of Opioids for the Treatment of Chronic Pain’” a component of the Opana ER Risk Map stated: “Misunderstanding of addiction and mislabeling of patients as addicts result in unnecessary withholding of opioid medications.” The Consensus Statement also misrepresented the rate of addiction stating,

⁴⁹² According to Endo’s RiskMAP, Endo distributed hardcopies of the book since mid-2004 and during 2005, an electronic version was posted to www.stoppain.org website. EPI000750035 at 17. In addition, copies of the book were mailed to participants in the NIPC’s Conference Line Series entitled: Advances in Opioid Analgesia: Maximizing Benefit While Minimizing Risk. *See, e.g.*, KP360_OHIOMDL_000052615.

⁴⁹³ ENDO_OPIOID_MDL-03862731 at 88.

“[s]tudies indicate that the de novo development of addiction when opioids are used for the relief of pain is low.”⁴⁹⁴

242.2. *A clinical guide to Opioid Analgesia* authored by Russell Portenoy, MD and Perry Fine, MD likewise downplayed the risk of addiction with opioids. Under the heading “Risk of Addiction,” it stated: “Overall, the literature provides evidence that the outcomes of drug abuse and addiction are rare among patients who receive opioids for a short period (ie, for acute pain) and among those with no history of abuse who receive long-term therapy for medical indications. The risk should not be assumed to be nil, however, and it may vary with specific characteristics of the patient.”⁴⁹⁵

243. In my opinion, Endo through its distribution of the AAPM/APS ‘Consensus Statement on the Use of Opioids for the Treatment of Chronic Pain’ and *A clinical guide to Opioid Analgesia* as part of the Opana ER Riskmap minimized the risk of addiction associated with Opana ER and opioids in general.⁴⁹⁶

⁴⁹⁴ This statement is also inconsistent with the launch label for Opana ER. At FDA’s request, Endo deleted similar language from the Opana ER label. *See* ENDO-OPIOID_MDL-00299009 at 1-2 (striking “[t]he development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients” from the label).

⁴⁹⁵ ENDO_OPIOID_MDL-03862731 at 40.

⁴⁹⁶ In addition to “Professional Education Initiatives,” Endo’s RiskMap for Opana ER represented to FDA that for “all of Endo’s controlled substance products, the manufacturing and distribution chain highly controlled and closely monitored.” EPI000750019 at 23. Endo further represented that its “oversight includes physical and administrative controls as well as significant monitoring activities.” *Id.* With regard to “Excessive Orders Management,” Endo told FDA that it flagged all orders as “excessive” for additional review if: (1) “the order exceeded the past 3 months average shipped quantity,” and /or (2) the order exceeded the past 12 months average shipped quantity by 15%. *Id.* at 43 (Appendix 3 to Opana ER Riskmap-Order Processing and Distribution). Endo’s Director of Customer Service and Distribution, Lisa Walker, confirmed the inadequacy of Endo’s oversight of the distribution chain. During her deposition, in response to the question whether “Endo ever reported suspicious orders for one of its branded products to DEA,” Ms. Walker testified “No, we have not.” Lisa Walker Depo Tr. 55:5-7, 10-11.

4. Endo's Promotion and Sales of Opana ER Increased as Reports of Abuse Grew.

244. During the five years that Endo promoted Opana ER, Endo increased its marketing expenditures by \$111,282,686⁴⁹⁷ with sales increasing from \$66,306,804 to \$1,028,255,461.⁴⁹⁸

245. As prescriptions and sales of Opana ER increased, Endo received increasing reports of abuse Opana ER abuse.

246. In as early as 2009, Endo received reports documenting addiction and abuse with Opana ER with reports increasing over time.

246.1. A March 23, 2009 email from Frank Yuen Clinical Affairs Manager regarding www.wate.com: Newport police: abuse of prescription drug Opana on the rise stated: "On Saturday I attended a Beth Israel Medical Center (New York) conference entitled: 'Emerging Practices in Opioid Prescribing for Chronic Pain.' During the morning Q & A session, a physician (Joe Browder, MD-Tennessee) . . . mentioned the 5 'Opana' deaths in Tennessee in recent times . . . He told me that all of the deaths were related to recreational use. One death was the result of an opioid naïve 18 year old getting hold of a relative's Opana and crushing it and snorting it . . . He also believed that the severe restrictions on OxyContin may have contributed to the experimentation with Opana. Dr. Browder said to the audience that his county was among those with the

⁴⁹⁷ END00000923 at slides 56-57 (2006 Opana Business Plan); EPI000560276 at slide 58 (2008-2012 Opana Brand Tactical Plan); EPI001474537 at slide 13 (Branded Pharmaceuticals Budget Overview); ENDO-CHI_LIT-00439415 at 53 (Branded Pharmaceuticals Business Review).

⁴⁹⁸ Endo sold Opana ER for part of 2012 and had sales of \$74,842,095.

highest incidence of OxyContin abuse in the country. Brian's name was not mentioned as a possible link to this *epidemic*.”⁴⁹⁹

246.2. A May 1, 2009 email from Heidi Higgins, Special District Manager for Endo, to John Doyle, Corporate Compliance and Business Practices Director for Endo regarding “Reports of Opana Abuse in the state of Ohio—Dr. Miles” sent with an importance level of “High” forwarded an OSAM-O-GRAM dated June 2008-January 2009, a document containing “key findings of the Ohio Substance Abuse Monitoring (OSAM) Network.” The document stated: “[u]sers in Athens and Cincinnati indicated that the Opana ‘high’ was comparable to or even better than that of OxyContin (oxycodone, extended release). A white female user in her 20s from Athens reported that her best friend had obtained a tablet illegally and inhaled it intranasally. She commented ‘And I guess you can really blow out of it, for less [than a tablet of OxyContin].’ Another white female in her mid-20s added, ‘*Right, I guess that’s like an Oxy times 10 . . .*’ A 30 year-old white female user from the Cincinnati region who was being treated for prescription opioid abuse stated that, ‘The oxymorphone is the best . . . even better than oxycodone. I can do a whole Oxy 80 [80 milligram strength tablet of OxyContin] and nothing happens, but if I take one of them pills [Opana ER] I can get a buzz; . . . that’s how I get the energy to do things around the *house*.’”⁵⁰⁰

246.3. A May 1, 2011 Drug Enforcement Administration Drug Intelligence Briefing for the Philadelphia stated “[t]he Philadelphia Division Intelligence Program received information on a possible emerging trend in the region; Oxymorphone (brand name Opana) has been reported by several sources of information as the ‘big thing right

⁴⁹⁹ END00361409.

⁵⁰⁰ ENDO-OPIOID_MDL-02178254 at 3.

now’ in pharmaceutical drug abuse in the region.” The Brief further noted “[s]lang terms for oxymorphone include: blues, biscuits, blue heaven, new blues (although the immediate-release tablets are pink and off-white), octagons (extended-release), [strength], octagons, stop signs, pink, pink heaven . . . pink heaven, pink lady, Mrs O, OM, Pink O, The O Bomb . . . and others.”⁵⁰¹

246.4. On August 16, 2011, Geoffrey Becker sent Timothy Byrne, senior director of public policy at Endo and colleagues an article from the Charleston WV Daily Mail entitled “Crushable pain medication a target for abusers.” The article stated: “Authorities are finding more people abusing prescription Opana, a drug that appeared on officers’ radars after OxyContin was reformulated late last year, said Charleston Lt. Chad Napier.” The article further stated “[t]he use of Opana started slowly climbing because Purdue Pharma was getting such bad press with the asset forfeitures and abuse statistics.”⁵⁰²

247. At the same time, Endo failed to use available information to detect unusual prescribing patterns that could indicate abuse or diversion of the drug.

247.1. A February 9, 2012 email from Alicia Logan, Brand Manager at Endo, to Javier Avalos, Senior Director of Channel Strategy in Endo’s Trade Group, included a list of “Pharmacies that stated REFUSAL-PRESCRIBING PHYSICIAN as a Decline Reason.”⁵⁰³

⁵⁰¹ ENDO-OR-CID-00694084.

⁵⁰² EPI000987149.

⁵⁰³ ENDO-OPIOID_MDL-00468003 at 1-2.

247.2. Included on the list of physicians for whom pharmacies refused to fill prescriptions was Dr. Oliver Herndon.⁵⁰⁴

247.3. According to a news report distributed internally at Endo, “Dr. Herndon prescribed Opana and other potent narcotics based on three-minute office visits devoid of physical examinations or case histories.”⁵⁰⁵

247.4. Despite the availability of information stating that pharmacies were refusing to fill prescriptions by Dr. Herndon to Endo’s trade group, Endo’s Vice President of Sales, Larry Romaine, testified at his deposition that he did not recall being aware that such information existed.⁵⁰⁶

247.5. Dr. Herndon, “the #1 prescriber of [Opana ER] in the nation” who was on Endo sales reps’ call list since at least 2010,⁵⁰⁷ remained on that list until November 2012 when he was removed because of “no access”⁵⁰⁸ after he pled guilty to healthcare fraud and improper distribution of oxycodone and oxymorphone.⁵⁰⁹

⁵⁰⁴ *Id.*

⁵⁰⁵ *Id.*

⁵⁰⁶ Larry Romaine Depo Tr. 217:3-15.

⁵⁰⁷ Larry Romaine Depo Tr. 381:23-382:3 (“Dr. Herndon ha[d] been detailed since at least 2010” as part of Endo’s “library program.”); *see also* ENDO-OPIOID_MDL-00817302 at 141.

⁵⁰⁸ ENDO-OPIOID_MDL-02924490 at 65.

⁵⁰⁹ ENDO-OPIOID_MDL-02314929 (June 18, 2012 email from Janett Mendez DeTore, Endo Region Business Director to Larry Romaine, Endo Vice President of Sales, forwarding Pittsburgh post-gazette.com news article with the same date reporting that Dr. Oliver W. Herndon had “pleaded guilty last month to health care fraud and improper distribution of oxycodone and oxymorphone.”).

248. Endo also received reports of healthcare provider prescribing levels for Opana ER, but based on testimony provided, did not use this information to look for unusual prescribing patterns that could indicate abuse or diversion of the drug.⁵¹⁰

248.1. Larry Romaine, Endo's Vice President of Sales, testified that "at any given period for a given product," information regarding which prescribers were prescribing the most product was available to him.⁵¹¹ Mr. Romaine agreed that such data could be looked at for "patterns of prescribing for individual doctors" including "whether that doctor's prescriptions were fairly high compared to other prescribers in any given territory."⁵¹²

248.2. Neither Mr. Romaine nor Brian Lortie, Endo's Senior Vice President and General Manager for Branded Pharmaceuticals,⁵¹³ however, could recall that such data was used to detect suspicious prescribing activity.⁵¹⁴

248.3. Mr. Lortie testified that "Endo certainly had policies and procedures to . . . measure prescriptions for its products" but could not "recall specifically" the "extent that that was used as part of an abuse and diversion mitigation process."⁵¹⁵

⁵¹⁰ The opioid manufacturers were in possession of detailed prescription data that included product information, such as dosage, number of units prescribed, the prescriber, geographic location of the prescriber and pharmacy, and method of payment. *See, e.g.*, PDD1502500909; E1247_ENDO-OPIOID_MDL-02924490; ACTAVIS0723709; JAN00114751; MNK-T1_0000106040.

⁵¹¹ Larry Romaine Depo Tr. 293:24-294:14.

⁵¹² *Id.* at 301:2-5, 8-13, 301:15-19-302:1.

⁵¹³ Brian Lortie Depo Tr. 28:19-24.

⁵¹⁴ Larry Romaine Depo Tr. at 303:18-304:4, 6-11, 304:22-305:6, 8.

⁵¹⁵ Brian Lortie Depo Tr. 159:12-19.

248.4. When asked to confirm that “it was not anyone’s specific job to proactively monitor . . . on a monthly basis sales data to see if it could detect any unusual patterns that may be indicative of a pill mill,” Mr. Lortie testified, he was “not sure.”⁵¹⁶

248.5. Mr. Lortie further testified that Endo “absolutely” did not “have a policy as part of its anti-diversion efforts by which sales reps were to actively go out and ask healthcare providers they were calling on whether those healthcare providers had suspicions about any pill mills that may exist in a territory that the sales rep served,” because the sales reps were not “law enforcement agents.”⁵¹⁷

248.6. Mr. Lortie was also unaware that Endo conducted “any due diligence . . . to see whether [a] healthcare provider might, in fact, be a pill mill” before adding a physician to a call list.⁵¹⁸

249. By 2012, Endo received reports that according to the Ohio’s Substance Abuse Monitoring Network “Opana was becoming popular as a replacement for OxyContin [in Akron, Cincinnati and Athens, Ohio] as it was easier to use.”⁵¹⁹ The report also noted that Opana 40 mg tablets had eclipsed street prices for OxyContin.⁵²⁰

250. That same year, Endo acknowledged its “contribution” to the opioid crisis:

250.1. At a 2012 Pain Management Summit, Neil Shusterman, Endo’s Director of Pharmacovigilance, stated: “[T]he old Opana was very, very easy to crush. Anybody in this room could easily do it by just taking their [fist] and reducing it to a powder on a

⁵¹⁶ *Id.* at 11-17, 20-21.

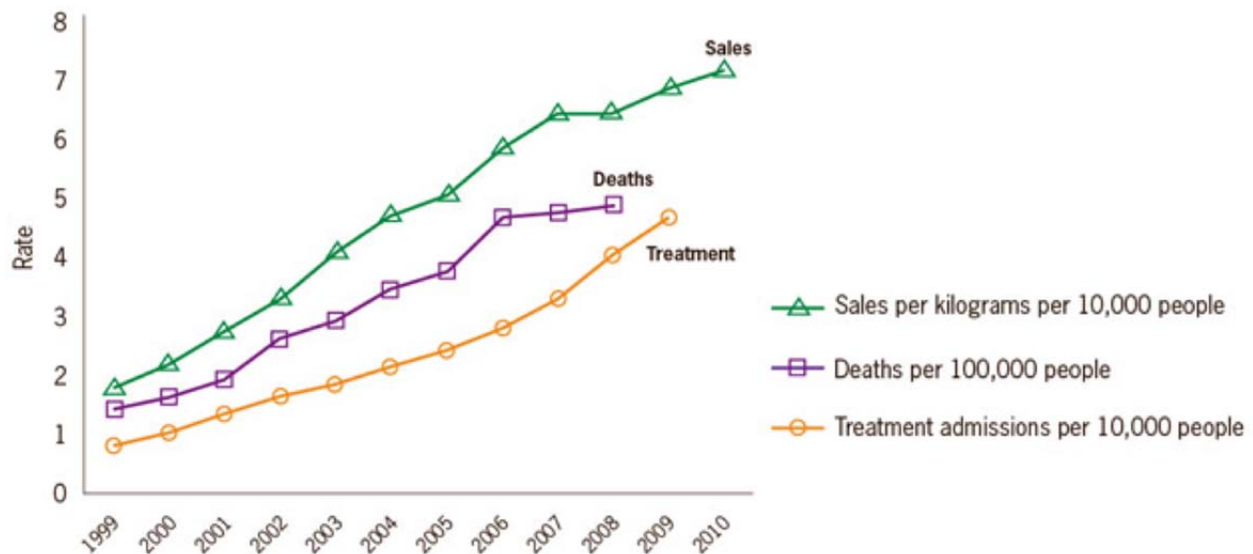
⁵¹⁷ *Id.* at 164:24-165:1-6, 8-12.

⁵¹⁸ *Id.* at 169:6-12, 14-19.

⁵¹⁹ EPI000832250.

⁵²⁰ *Id.*

tabletop. And therein lay the problem as I'll get to because nasal insufflation, snorting was the major route of abuse with Opana. And we felt therefore we needed to come up with a technology that would make it harder."⁵²¹ Referring to a chart from the National Vital Statistics System on Rates of Prescription Pain Killer Sales, Deaths and Substance Abuse Treatment Admissions from 1999-2010,⁵²² Mr. Shusterman stated "Everybody's seen this slide. I don't see how any of these talks can start without showing the magnitude of the problem. And we felt that being responsible to what we knew to be our specific contribution to the problem was the right thing to do."⁵²³



251. In my opinion, Endo's promotion and sales of Opana ER increased as reports of abuse grew.

⁵²¹ END00649416 at 167.

⁵²² END00648960 at 38. Mr. Shusterman's slide deck contains a black and white version of the above chart. For improved readability, a color version of the same chart obtained from <https://www.cdc.gov/vitalsigns/painkilleroverdoses/> (the same source noted on Mr. Shusterman's slide) is included above.

⁵²³ *Id* at 168.; END00648960 at 38.

D. Opana ER Reformulated

1. Endo's Marketing Strategy for Opana ER Reformulated

252. An important purpose in developing Opana ER reformulated was to replace Opana ER original, which would face generic competition. As described in a 2007 Endo document, “a TRF formulation of ER will be important to secure” “[t]o ensure we continue to protect the franchise in the face of loss of regulatory exclusivity in 2009 . . . Without this LCM strategy, Opana ER is expected to lose about 70% of its sales within six months if generic entry occurs.”⁵²⁴

253. A distinction between the reformulated Opana and the original formulation was that it was made with Intac technology. Intac technology, developed by Grunenthal GmbH, is “[a] manufacturing process that [combines] an active drug (oxymorphone HCl) with a [polyethylene oxide (PEO)] of high molecular weight above the PEO melting point and simultaneously [applies] force on the heated mass.”⁵²⁵

2. FDA Denial of Abuse Deterrent Claim as to Opana ER Reformulated

254. Endo sought to obtain approval of Opana ER reformulated with abuse-deterrent labeling claims.⁵²⁶

254.1. During Pre-IND Meetings with FDA, Endo learned that “[n]o claims of abuse deterrence or resistance will be allowed based on tablet hardness.”⁵²⁷

254.2. Early on in the development of the reformulated drug, initial testing of the reformulated opioid supported the conclusion that “TRF can be overcome with additional

⁵²⁴ ENDO-CHI_LIT-00176743 at 1.

⁵²⁵ ENDO-CHI_LIT-00227354 at 9.

⁵²⁶ See ENDO-OR-CID-01174358 at 1-3.

⁵²⁷ ENDO-CHI_LIT-00020555 at 3.

time, effort, and money” and “[p]ossible weaknesses” included “i.v. and tablet heated in liquid.”⁵²⁸

254.3. On December 27, 2010, FDA removed a description of the physiochemical properties from the proposed label of Opana ER reformulated because FDA “felt the text suggests an impermeability to manipulation which the Division doesn’t believe is the case.”⁵²⁹

254.4. On January 4, 2011, based on the FDA’s review of Endo’s studies for Opana ER Reformulated, FDA provided Endo with its preliminary conclusion that an abuse-deterrent labeling claim was not warranted, stating “[Opana ER] provides limited resistance to physical and chemical manipulation for abuse. Revopan’s extended-release mechanism can be overcome by cutting, chewing, or grinding . . . [Opana ER reformulated] tablets provide some resistance to crushing using simple tools such as two spoons, a pill crusher or hammer.”

254.5. In this letter, FDA also stated that “[t]he product label should not include language asserting that [Opana ER] provides resistance to crushing, because it may provide a false sense of security since the product may be chewed and ground for subsequent abuse.”⁵³⁰

255. After receiving the January 4, 2011 letter from FDA, Endo amended its NDA for Opana ER and to remove its request for approval of an abuse deterrent labeling claim.”⁵³¹

⁵²⁸ ENDO-CHI_LIT-00064407 at 6.

⁵²⁹ EPI001313732 at 2.

⁵³⁰ *Id.* at 2- 3.

⁵³¹ Endo later again sought approval of an abuse deterrent labeling claim for Opana ER Reformulated but did not receive FDA approval for such a claim.”

3. Endo Marketed Opana ER Reformulated as “Crush Resistant” Despite FDA’s Instruction Otherwise

256. Endo’s launch materials included claims regarding the physiochemical properties of Opana ER reformulated suggesting that the reformulation was safer than the old version. FDA took issue with these launch materials. Specifically, in an April 30, 2012 letter from Samuel M. Skariah, Regulatory Review Officer in the Division of Drug Promotion (“DPDP”) Office of Drug Promotion at FDA to William A. Best, Sr., Director Promotional Regulatory Affairs raised concerns that Endo’s promotional launch materials for Opana ER Reformulated suggested a therapeutic advantage not supported by substantial evidence.⁵³² The letter from DPDP stated:

256.1. “The proposed detail aid contains numerous claims and presentations describing Opana ER’s new formulation and its INTAC™ technology . . . the totality of [which] suggest that, as a result of its new formulation Opana ER offers a therapeutic advantage over the original formulation when this has not been demonstrated by substantial evidence or substantial clinical experience.”

256.2. “For example, page two includes claims such as the following: ‘**INTAC™ technology provides mechanical stability,**’ ‘Innovative manufacturing process uses heat extrusion to create mechanical strength’ (page 2); ‘New formulation of Opana ER tablets with INTAC technology has the mechanical; strength to provide an obstacle to crushing by tools, including hammers, spoons, and mechanical pill crushers’”

256.3. “Additionally, page three includes claims and presentations such as the following regarding a blinded comparative study in 25 subjects (bolded emphasis in original: ‘**Opana ER with INTAC™ technology compared to oxymorphone ER**

⁵³² ENDO-CHI_LIT-00015924

(original formulation) . . . Provided some resistance to crushing by tools, including spoons, a hammer, or a razor””

256.4. “**Manipulating Opana ER tablets with INTAC™ technology resulted in larger particle size than oxymorphone ER** (original formulation)’ (with accompanying visual); ‘Study demonstrated the difficulty in forming an intranasal preparation’ (with accompanying visuals)”

256.5. FDA’s letter clarified that statements such as “[t]he clinical significance of INTAC technology or its impact on abuse/misuse has not been established for the new formulation of Opana ER’ on various pages of the piece” did “not mitigate the overwhelming misleading impression” of the detail aid.

256.6. Finally, FDA advised: “[w]e are especially concerned from a public health perspective because the presence of this information in the detail aid could result in health care practitioners or patients thinking that the new formulation is safer than the old formulation, when this is not the case.”⁵³³

257. Despite FDA’s letter concerning Endo’s launch materials for Opana ER reformulated, Endo agreed on a promotional strategy for Opana ER reformulated on May 15, 2012 that included the phrase “Designed to be crush resistant,” acknowledging that this strategy risked a warning letter from FDA.⁵³⁴

258. Endo also trained its sales reps to promote Opana ER Reformulated as designed to be crush resistant. For example, a May 2012 sales training aid stated:

⁵³³ *Id.* at 2.

⁵³⁴ ENDO-OR-CID-00345837 at 1; A December 12, 2011 press release announcing FDA approval of Opana ER Reformulated stated: “Endo Announces FDA Approval of a New Formulation of Opana ER Designed To Be Crush-Resistant.” ENDO-CHI_LIT-00002025 at 1.

The **ONLY approved** message that you can proactively communicate with your HCPs regarding the INTAC Technology is: “INTAC Technology is designed to be crush resistant. However, the clinical significance of INTAC Technology or its impact on abuse/misuse has not been established for Opana ER. Opana ER has an abuse liability similar to other opioid analgesics as stated in the boxed warning.”⁵³⁵

259. By 2013, Endo’s message that Opana Reformulated was “crush resistant” had been delivered to healthcare providers:

259.1. A June 7, 2013 Opana ER with INTAC 2013 Research Report reported the following regarding healthcare providers “Perception and Usage of [Opana ER Reformulated]: “Many HCPs express concern about patient safety. They feel Opana ER is superior to oxymorphone HCI ER because of its crush-resistant formula. They would prefer to use Opana ER, if possible.” The Report also stated that “Some HCPs recall hearing” that Opana ER is “Crush-resistant/tamper proof” with one physician reporting that “[t]hey’ve told me it’s designed to be crush-resistant and that is a big deal. I want all of my patients to [] have as little potential for abuse as possible.”⁵³⁶

259.2. A slide entitled “Perception and Usage of Opana ER” in an Opana ER with INTAC 2013 Research Q2 Qualitative Research Report dated June 7, 2013 stated: “Some HCPs recall hearing the following information recently about Opana ER (2+ mentions)”: Crush-resistant/tamper-proof.”⁵³⁷

259.3. Endo likewise promoted and positioned Opana ER Reformulated to Compendia. As described in a December 2012 Compendia status update from “[a]ll 3 Data Compendia have uniquely classified Opana ER with INTAC technology based on the dosage form of Crush Resistant . . . With a unique classification, Opana ER

⁵³⁵ ENDO-CHI_LIT-00271332 at 1.

⁵³⁶ END00591813 at 9-10.

⁵³⁷ END00591813 at 10.

prescriptions have a much lower probability of being switched at the pharmacy with non-CRF generic formulation.”⁵³⁸

260. In my opinion, Endo marketed Opana ER as “Crush Resistant” despite FDA’s instruction otherwise.⁵³⁹

4. Despite Increasing Evidence of Abuse of Opana ER Reformulated, Endo Continued to Promote Opana ER Reformulated in the Manner Described Above and Thus Put the Public Health At Risk.⁵⁴⁰

261. In 2012 and 2013, sales of Opana ER Reformulated increased from \$221,550,787 to \$222,796,458⁵⁴¹.

262. As prescriptions of Opana ER Reformulated increased, Endo received increasing reports of abuse.

262.1. A November 19, 2012 NAVIPRO Addiction Vigilance Intervention and Prevention Program Report stated “Review of data from the ASI-MV indicated that during Q3 2012, past 30-day abuse of reformulated Opana ER was reported at a level comparable to that of the original version of the product and most frequently via oral ingestion (i.e., by swallowing the tablet whole) and injection . . . These initial observations from NAVIPPRO during this transition period suggest that the reformulated product may have a different abuse profile than the original formulation.”⁵⁴²

⁵³⁸ EPI002485011 at 4, 6. Endo discontinued use of “designed to be crush resistant” claim after denial of Citizen Petition. (Kristin Vitanza Depo Tr. 481:2-8, 17-22)

⁵³⁹ See also EPI002485011 at 4. (Endo Compendia Status Updated stated “[a]ll 3 Data Compendia have uniquely classified Opana ER with INTAC technology based on the dosage form of Crush Resistant.”)

⁵⁴⁰ Endo discontinued the promotion of Opana ER Reformulated as “designed to be crush-resistant” as of May 2013. See END00126255 at 3; see also Kristin Vitanza Depo. Tr. 481:2-8, 11-22 (Endo discontinued use of “designed to be crush resistant” claim in promotion of Opana ER Reformulated after FDA’s denial of Endo’s citizen petition).

⁵⁴¹ ENDO_DATA-OPIOID_MDL-00000014; ENDO-DATA-OPIOID_MDL-00000016.

⁵⁴² ENDO-OR-CID-00829694 at 9.

262.2. A February 5, 2013 NAVIPPRO Epidemiology Programs Study Report stated “reports of abuse of the reformulation via alternate routes of administration (i.e., particularly injection) continue to be observed.”⁵⁴³

262.3. In a May 10, 2013 response to a supplemental new drug application submitted by Endo seeking an abuse deterrent labeling claim, FDA stated that postmarketing data was insufficient “to support any conclusion about the overall or route-specific rates of abuse of Opana ER.” However, FDA noted “if the early trends in postmarketing data . . . are supported by data from further assessments, it would appear that a reduction in abuse by insufflation may be accompanied by a rise in intravenous abuse. This would be a transition to a more dangerous behavior, as intravenous abuse is associated with a greater risk of infection, including hepatitis, HIV and bacterial pathogens, along with a greater risk for overdose and death.”⁵⁴⁴

262.4. On March 13-14, 2017, the majority of a Risk Management Advisory Committee and the Anesthetic and Analgesia Drug Products Advisory Committee Joint Meeting voted “No,” “indicating their belief that the benefits of reformulated Opana ER do not continue to outweigh its risks.”⁵⁴⁵

262.5. On June 8, 2017 FDA advised Endo “it believes the benefits of reformulated Opana ER no longer outweigh the risks that accompany the product,

⁵⁴³ ENDO-OPIOID_MDL-00350952 at 28.

⁵⁴⁴ ENDO-OR-CID-01174358 at 2.

⁵⁴⁵ Summary Minutes of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesia Drug Products Advisory Committee Joint Meeting Mar. 13-14, 2017 available at: <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM551226.pdf> (last visited Mar. 12, 2019).

therefore Endo should voluntarily cease marketing Opana ER.”⁵⁴⁶ During the meeting, “Endo agreed to stop manufacturing of the drug product immediately and cease shipping by August 31, 2017.”⁵⁴⁷

263. In my opinion, despite increasing evidence of abuse of Opana ER Reformulated, Endo continued to promote Opana ER Reformulated in the manner described above and thus put the public health at risk.⁵⁴⁸

VII. JANSSEN

A. Overview

264. Janssen has promoted and sold opioid products known as Duragesic, Nucynta IR, and Nucynta ER.

265. As set forth below, Janssen contributed to the change in the practice of medicine with regards to pain treatment, and the concomitant expansion of both the use and abuse of opioids, by misleading promotion and marketing that minimized the risks and overstated the benefits of its opioid drugs.

⁵⁴⁶ ENDO-OPIOID_MDL-01831503 at 3. As discussed above, information available to Endo in 2009 indicated that injection was another potential route of abuse for Opana ER Reformulated. *See* ENDO-CHI_LIT-00064407; ENDO-CHI_LIT-0006790118.

⁵⁴⁷ *Id.* at 4. Weeks before the withdrawal, Endo offered wholesaler customers 20% off their purchases of the soon-to-be withdrawn drug. *See* ENDO-OPIOID_MDL-02290107 at 1-2 (approving of Opana ER Wholesaler Promotion).

⁵⁴⁸ Endo took some steps to address reports of abuse, but they were limited. *See, e.g.*, EPI000727600 at 3 (public service announcement in 97 movie theatres in Tennessee beginning on March 1, 2013); ENDO-OR-CID-00969795 (educational materials distributed to healthcare providers in Tennessee).

B. Duragesic

1. Regulatory Background

(a) Relevant labeling history

266. Duragesic is a fentanyl transdermal patch manufactured and marketed by Janssen. The patch provides continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours.⁵⁴⁹

267. Duragesic was first approved in August 1990 for “the management of chronic pain in patients requiring opioid analgesia.”⁵⁵⁰ The indication stated that Duragesic was not recommended in the management of postoperative pain.⁵⁵¹ The label also carried the precaution that all doses except the lowest Duragesic dose, 25 µg/h, “are too high for initiation of therapy in non opioid-tolerant patients and should not be used to begin Duragesic therapy in these patients.”⁵⁵²

268. In January 1994 the indication in the label was updated to “the management of chronic pain in patients who require *continuous* opioid analgesia for pain *that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids.*”⁵⁵³

269. A statement that Duragesic is contraindicated in the management of acute or post-operative pain was added to the contraindications section by 1998, as was a statement that Duragesic was contraindicated in “the management of mild or intermittent pain that can otherwise be managed by lesser means such as acetaminophen-opioid combinations, non-

⁵⁴⁹ JAN-MS-00238727.

⁵⁵⁰ JAN-MS-00238727; JAN-MS-00551711.

⁵⁵¹ JAN-MS-00238727.

⁵⁵² JAN-MS-00238727.

⁵⁵³ JAN00221820 at 32 (emphasis added for significant changes).

steroidal analgesics, or PRN dosing with short-acting opioids.”⁵⁵⁴ The label was also updated by this time to state that Duragesic was contraindicated “in doses exceeding 25 µg/h at the initiation of opioid therapy.”⁵⁵⁵

270. In February 2005, the indication changed again to “management of *persistent, moderate to severe* chronic pain that cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate release opioids.”^{556 557}

271. In 2005, a black box warning was added stating **“FOR USE IN OPIOID-TOLERANT PATIENTS ONLY”** and **“DURAGESIC_® should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC_® 25 mcg/h.”**⁵⁵⁸ This same language was restated in the updated indications, and a contraindication was added stating that Duragesic is contraindicated “in patients who are not opioid-tolerant.”⁵⁵⁹

272. This change essentially extended the restriction in the indication for opioid-naïve patients from doses higher than 25 mcg to *all* doses, including the lowest dose. At the same time, a new 12 mcg/h titrating dose was introduced.⁵⁶⁰

⁵⁵⁴ JAN-MS-00907134 at 7-8.

⁵⁵⁵ JAN-MS-00907134 at 8.

⁵⁵⁶ Duragesic label, February 2005, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/19813s039lbl.pdf (last visited March 19, 2019) (emphasis added for significant changes).

⁵⁵⁷ Later changes to the indication, after generic Duragesic/fentanyl patches became available, are contained in Schedule 12.

⁵⁵⁸ JAN00222123 at 1 (emphases in original). The label defined patients who are considered opioid-tolerant as “those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.”

⁵⁵⁹ JAN00222123 at 2.

⁵⁶⁰ JAN00222123 at 2.

(b) Pre-Approval FDA Correspondence

273. The FDA Medical Officer Review (“MOR”) of the NDA for Duragesic was authored by Dr. Curtis Wright.⁵⁶¹ Even before reviewing the NDA for Duragesic, Dr. Wright raised concerns with Janssen about diversion of the product.⁵⁶² At a pre-approval meeting with Janssen in August 1989, he asked about “the potential for extraction of fentanyl from used or unused systems” and suggested “ways to reduce the abuse potential,” including incorporation of naloxone.⁵⁶³

274. At a subsequent pre-approval meeting with Janssen regarding abuse liability and diversion issues with Duragesic, Dr. Wright also advised Janssen that it would “need special precautions to keep this product on target for the cancer pain population.”⁵⁶⁴

275. In the Duragesic MOR, Dr. Wright noted, “It is the opinion of the reviewer that once the clinicians learn that the TTS [Transdermal Therapeutic System] fentanyl system can provide continuous opioid analgesia through the night, that the system will be used in a much broader clinical population than intended. This spread beyond the use which has been evaluated in clinical trials is common to many drugs and represents an unknown hazard for all of them. It is not unsafe, by itself, but the extent of such use should be estimated, the risks identified, and their management outlined.”⁵⁶⁵

276. Dr. Wright also stated in the MOR that “[i]n the opinion of the reviewer, the system is approvable, but will require Phase IV obligations to be placed on the sponsor to ensure

⁵⁶¹ As noted in the Purdue section above, Dr. Wright later authored the Medical Officer Review of the NDA for OxyContin and ultimately left FDA to work for Purdue Pharma.

⁵⁶² JAN-MS-02908031.

⁵⁶³ *Id.*

⁵⁶⁴ JAN-MS-02909945 at 3.

⁵⁶⁵ JAN-MS-00551711 at 316.

that the introduction of the system into clinical practice is not accompanied by extensive improper use and consequent morbidity and mortality. The available data shows that use of the TTS fentanyl system will result in an increased total opioid dose to the patient over PRN dosing, which is a major advantage in clinical situations where under-dosing is the norm. If TTS fentanyl use is extended to clinical situations where this is not the case, opiate over-dosage is likely to occur. As use of the system spreads beyond the post-operative period and the “healthy” cancer patient it will be given to patients who are receiving concomitant medications which affect respirations and serious adverse events due to drug-drug and drug-disease interactions will occur. It is not possible on the basis of the available data to predict the probable frequency or severity of these reactions, but the advertising and detailing of the system will be critical in preventing overdose attributable to its use.”⁵⁶⁶

277. I have been unable to locate in the record any evidence that Janssen conducted Phase IV studies into improper use and consequent morbidity and mortality.

278. Dr. Wright further stated in his “safety conclusions” section regarding clinical trials of Duragesic that trials in postoperative settings revealed the adverse event of respiratory depression at rates of 3% to 6%. Dr. Wright stated, “It may reasonably be expected that the frequency of this adverse effect will increase should TTS use spread into more debilitated populations on the medical services and into less well supervised postoperative settings.”⁵⁶⁷

279. The “Dissolution Review Portion” of FDA’s review of the Duragesic NDA appears to have stated that the studies of Duragesic “indicate that all of the TTS patches deliver more fentanyl than expected. From the data presented by the sponsor concerning residual fentanyl, it can be shown that, on the average, all of the subjects in the studies received 150% of

⁵⁶⁶ *Id.*

⁵⁶⁷ *Id.*

the target dose in 24 hours. This excessive release of fentanyl can have significant consequences (safety) given that the fentanyl has a narrow therapeutic range.”⁵⁶⁸

280. As demonstrated below, many of Dr. Wright’s predictions came true. Duragesic was used in a “much broader clinical population than intended,” due to Janssen’s improper marketing of the drug for broader indications, its understatement of the risks of the drug in its promotions, and its overstatement of its benefits. Because of this improper marketing, Duragesic use was in fact extended to clinical situations beyond where under-dosing is the norm, substantial numbers of overdoses did occur, and excessive release of Duragesic did have significant safety consequences. Spurred by Janssen’s marketing, use of Duragesic did spread beyond the post-operative period and the “healthy” cancer patient. While Dr. Wright considered advertising and detailing of Duragesic critical to preventing overdoses, that depends on it being careful and accurate; the misleading nature of the advertising and detailing Janssen actually employed in fact made overdoses and abuse more likely.

2. Janssen’s Marketing of Duragesic Broadened its Indications, Expanding the Use of Long Acting Opioids and Contributing to the Change in the Practice of Medicine.

(a) Janssen’s Marketing Focus Shifted from Cancer Pain to Non-Cancer Chronic Pain in the Mid-1990s.

281. The initial focus of Janssen’s marketing of Duragesic was on cancer patients. A “Positioning Evolution Overview” dated June 2002 provides a “Duragesic Ad Campaign Overview” timeline that tracks the evolution of the drug’s marketing. The first entry in the timeline, for March 1991, is “Focus on introduction of patch technology providing 72 hours of relief to malignant chronic pain patients.”⁵⁶⁹

⁵⁶⁸ JAN-MS-02908681 at 7-8. The stand-alone document could not be located in the documents produced by Janssen.

⁵⁶⁹ JAN-MS-00309606 at 7.

282. Starting in the mid-1990s, at around the same time that Purdue introduced OxyContin CR, Janssen's promotion of Duragesic shifted from a focus on cancer pain to chronic pain generally, and introduced comparisons to oral opioids. The "Duragesic Ad Campaign Overview" timeline noted that as of May 1994 there was a "Shift away from limiting consideration to only malignant patients" to "Promotion of around-the-clock control highlights benefits of 72 hour efficacy in limiting breakthrough pain associated with oral medications."⁵⁷⁰

283. A Duragesic "Journal Advertising Overview" shows that from April 1995 to July 1997, Janssen's "Core Campaign Journal Ad" for Duragesic used the headline "Why Interrupt These Moments With Oral Opioid Dosing?" and the tagline "Chronic Pain Control That Goes On."⁵⁷¹

284. A November 12, 1999 bulletin Janssen sent to its Sales Force reported on an article in the British Medical Journal regarding a physician who was disciplined for undertreating pain.⁵⁷² The bulletin noted, "One of the issues that is driving the rapid expansion of the pain market is the changing attitude towards the treatment of chronic, severe pain. While many physicians are becoming more comfortable with opioids and more aggressive treatment options, there are still situations where patients do not receive the treatment they need."⁵⁷³ The bulletin told the Sales Force that the case "underscores the importance of what you do on a daily basis...."⁵⁷⁴

⁵⁷⁰ *Id.*

⁵⁷¹ JAN-MS-00305469 at 5-7.

⁵⁷² JAN-MS-02728546.

⁵⁷³ *Id.*

⁵⁷⁴ *Id.*

285. A Duragesic Business Plan for 2001, dated 2000, stated that Duragesic's "vision" was to be the "first choice of chronic pain patients for around-the clock-therapy."⁵⁷⁵ The Plan noted that "Non-malignant market is the growth opportunity," but stated just below this point that "DURAGESIC data is non-existent."⁵⁷⁶ A SWOT analysis in the same document stated that "opioid acceptance for non-malignant pain" was an opportunity for Duragesic, but that "limited clinical data" was a weakness. Elsewhere in the same plan is the statement "need non-malignant pain data (lower back, OA [osteoarthritis]/RA [rheumatoid arthritis])."⁵⁷⁷

286. In May 2000, Janssen approached FDA's Division of Drug Marketing, Advertising and Communications (DDMAC) about its plan to do Direct to Consumer (DTC) advertising for Duragesic. While Janssen ultimately decided after several meetings with FDA not to pursue the DTC advertising plan,⁵⁷⁸ the interactions between it and DDDMAC regarding the plan highlight the shifting focus in Duragesic's promotion from malignant pain treated by pain specialists to non-malignant pain.

287. DDMAC's initial response to Janssen's DTC advertising plan was that it "[wa]s not thrilled by the idea but there [we]re no regulations preventing us from moving forward."⁵⁷⁹ At Janssen's next meeting with FDA regarding the plan, DDMAC Branch Chief Dr. Nancy Ostrove "expressed a concern about the patient population being targeted" and noted her "recollection was that we would target cancer patients."⁵⁸⁰ Janssen's representative "clarified" that Janssen's "market research had identified back pain and arthritis pain suffers as undertreated and

⁵⁷⁵ JAN-MS-00618253 at 3.

⁵⁷⁶ *Id* at 19.

⁵⁷⁷ *Id* at 18.

⁵⁷⁸ JAN-MS-00480543.

⁵⁷⁹ JAN-MS-00479787 at 2.

⁵⁸⁰ JAN-MS-00479784 at 2.

potentially appropriate candidates for Duragesic.” DDMAC’s representative responded that “this was fine but the message needs to be clearer that the drug is for severe pain, not ‘your everyday back pain.’”⁵⁸¹

288. At the next meeting between Janssen and FDA, Dr. Ostrove raised FDA’s concern that “Duragesic is currently being used by physicians experienced with pain management, who are comfortable with using and prescribing Duragesic. DTC would likely increase use by primary care physicians who are inexperienced with the product. This leads to FDA’s concern of increased inappropriate use and increased adverse events.”⁵⁸² Dr. Ostrove also suggested Janssen advise patients in the DTC ads “that their doctor may not be the right person to prescribe Duragesic and they may need to be referred to a specialist. This is particularly important as it will likely be the opioid-naïve patients who are going to their primary care physician as a result of the ad.”⁵⁸³

289. In a June 2001 presentation to Janssen by Discovery NJ entitled “Growing Market Share in 2002--Medical Education Tactics in Support of Duragesic,” “Expand Duragesic use in non-malignant pain” is identified as a “Key Strategy” for which “Role/Importance of Education” is shown as “High.”⁵⁸⁴ “Supporting tactics” for this key strategy include a “National CME Initiative;” a “KOL Development and Management Plan;” a plan to target particular publications such as JAMA with articles on Duragesic, including suggestions of possible titles, authors, and key messages; and a speakers’ bureau.⁵⁸⁵

⁵⁸¹ *Id.*

⁵⁸² JAN-MS-00479781 at 2.

⁵⁸³ *Id.*

⁵⁸⁴ JAN-MS-00780131 at 3.

⁵⁸⁵ *Id.* at 4, 7.

290. A 2003 “Duragesic Public Relations Activities” PowerPoint identified “Expand in non-malignant pain categories (back pain)” as a “Core Duragesic Brand Strategy,” and “Target non-malignant severe chronic pain states (primarily lower back)” as a “2003 PR Objective.”⁵⁸⁶

290.1. Under “Direct-to-Patient Awareness,” the presentation advocated that Janssen “[u]se broad, unbranded messages and stories about serious chronic back pain to attract potential patients,” and “[d]raw potential patients to ‘opt-in’ to branded Duragesic information on Internet.”⁵⁸⁷

290.2. It further suggested creating a website called www.chronicbackpain.com to “utilize Internet to engage, capture chronic back pain patients.”⁵⁸⁸

290.3. The PR plan explained that the “primary emphasis on lower back pain” was because “[a]long with osteoarthritis” lower back pain was “identified as key growth opportunity,” but “[u]nlike OA, chronic back pain is not ‘owned’ by any medication or pharmaceutical company.”⁵⁸⁹

291. A September 2003 presentation for Janssen by marketing firm ZS Associates entitled “Duragesic® PhysPulse® Brand Monitoring and Performance Enhancement Study” identified “a significant opportunity for greater Duragesic usage for applications outside of cancer pain, especially back pain.”⁵⁹⁰

⁵⁸⁶ JAN-MS-00776219 at 4.

⁵⁸⁷ JAN-MS-00776219 at 17.

⁵⁸⁸ JAN-MS-00776219 at 9-15.

⁵⁸⁹ JAN-MS-00776219 at 8.

⁵⁹⁰ JAN-MS-00306124 at 6, 43.

291.1. The presentation further urged that “Moving back pain from an opportunity area to a core application is an important objective for the brand,” and “Similar opportunities may be present in fibromyalgia, arthritis and neuropathic pain.”⁵⁹¹

291.2. The presentation suggested that “A shift in targeting and detailing frequency from Oncologists to PCPs and Pain Specialists may be required to drive greater consideration of Duragesic for these applications.”⁵⁹²

(b) Janssen’s Marketing Misrepresented Duragesic’s Efficacy and Risks for Chronic Non-Cancer Pain.

292. Janssen sent its sales force bulletins and training materials alerting them to studies of Duragesic for chronic non-cancer pain, and used professional file cards and similar materials in marketing that touted these studies.⁵⁹³ These promotional materials highlighted and at times overstated the studies’ positive findings for chronic non-cancer pain, while at times providing explanations for negative findings that attributed them to alleged flaws in the study design or in treatment, or to pre-existing conditions in the subjects. FDA’s DDMAC sent Janssen warning letters relating to misrepresentations it made regarding these studies in its promotional materials.

293. Janssen sent a September 2001 memorandum to its Field Sales Force regarding a study by Milligan et al. published in the *Journal of Pain* entitled “Evaluation of Long-term Efficacy and Safety of Transdermal Fentanyl in the Treatment of Chronic Noncancer Pain,”⁵⁹⁴

⁵⁹¹ JAN-MS-00306124 at 37, 43.

⁵⁹² JAN-MS-00306124 at 43.

⁵⁹³ JAN-MS-02728460 (bulletin re Simpson study); JAN-MS-00776447 (Duragesic self-study guide for sales representatives); JAN-MS-00776565 (bulletin re Milligan study); JAN-MS-00299212 (file card); JAN-MS-02757939 (file card); JAN-MS-02757751 (sales aid for sales representatives); JAN-MS-02757589 (sales aid for sales representatives).

⁵⁹⁴ JAN-MS-00311759.

and an editorial in response by Perry Fine.⁵⁹⁵ Janssen advised the Sales Force that the study's authors stated that Duragesic provided "stable, sustained, long-term pain control,"⁵⁹⁶ although the study had found that 1/3 of its subjects did not respond to Duragesic. Janssen explained this fact by stating that it "coincided with Perry Fine's comments (see editorial) that a process of trial and error is often needed to achieve adequate pain management."⁵⁹⁷ With regards to the study's reported global efficacy rate of 42%, Janssen advised its Sales Force that "[a] possible explanation for the low rate of global efficacy is that... the results for the global efficacy measurement did not include a "moderate" rating,"⁵⁹⁸ an explanation not offered by the study itself.

294. As to the study's reported withdrawal (drop-out) rate of 43%, Janssen's advised its Sales Force that the study's authors found "the incidence of AEs [adverse events] and the rate of withdrawal from the trial are relatively high but neither unusual nor unexpected considering the baseline clinical status of the study population."⁵⁹⁹ The Bulletin further advised the Sales Force that the fact that withdrawals due to adverse events or insufficient response diminished after 6 months "may indicate that most of the withdrawals [were] secondary to insufficient response or AEs may be related to improper titration and lack of tolerability to the transient side effects of TDF [transdermal fentanyl, i.e., Duragesic],"⁶⁰⁰ again an explanation not found in the study.

⁵⁹⁵ PPLPC020000014935 (Fine P.G., Opioid selection: plaudits, pitfalls, and possibilities. *Journal of Pain*. 2(4) August, 2001: 195-6.)

⁵⁹⁶ JAN-MS-00776565 at 3.

⁵⁹⁷ See JAN-MS-00776565.

⁵⁹⁸ *Id.*

⁵⁹⁹ *Id.*

⁶⁰⁰ *Id.*

295. Canadian health authorities had previously commented to Janssen that the studies it submitted in support of the use of Duragesic for chronic pain, including the Milligan study, involved only patients who were already taking potent opioids before entering the studies.⁶⁰¹ The Canadian authorities further noted that “the treatment of opioid naive patients with transdermal fentanyl for postoperative pain has resulted in deaths due to respiratory depression in the past.”⁶⁰² In its reply to the Canadian comments, Janssen stated “We acknowledge that the experience in opioid naive non-cancer patients is limited.”⁶⁰³ No such acknowledgement was made in Janssen’s Bulletin to its Sales Force about the Milligan study.

296. Janssen also did not advise its Sales Force in the Bulletin that the stability of pain control achieved in the study came at the cost of a near doubling of the mean dose of Duragesic over 12 months, even with unlimited access to rescue dosing.⁶⁰⁴ The Bulletin further did not disclose that the Milligan study had reported 3 cases of drug abuse/dependence (a rate of 1%), and 11 cases of opioid withdrawal syndrome (a rate of 3%)⁶⁰⁵ or that Janssen scientists had previously concluded based on analysis of data from the study that the “probability of tolerance with long term Duragesic use was low but not negligible,” with the global tolerance probability stated as 22%, and higher in those whose underlying disease deteriorated (28%) or improved (32%).⁶⁰⁶ This prior tolerance analysis, dated February 2001, found based on the Milligan study’s data that tolerance developed between 1 and 3 months of Duragesic use, and therefore

⁶⁰¹ JAN-MS-00901369 at 12.

⁶⁰² *Id.*

⁶⁰³ *Id.*

⁶⁰⁴ JAN-MS-00311759 at 6.

⁶⁰⁵ JAN-MS-00311759 at 5-6.

⁶⁰⁶ JAN-MS-00901949 at 4-5.

recommended that a guideline for long term treatment monitoring be introduced, with dose increases triggering reevaluation of the underlying disease.⁶⁰⁷

297. The Janssen scientist who co-authored the tolerance analysis above, Birgitte Kuperwasser, Associate Director of Global Analgesia R&D, later sent an email to other Janssen employees in which she noted that the Milligan study (referred to in her email as FEN-INT-13) was an “open single arm study to evaluate long term safety,” and stated that she wanted to “reiterate” concerns that had been raised previously regarding using the Milligan study (as well as two other post-marketing studies) “to make an argument for efficacy.”⁶⁰⁸ In (re)raising these concerns, Dr. Kuperwasser noted that “[t]hese studies have not [sic] the appropriate design neither the end points to make a case for efficacy.”⁶⁰⁹ Janssen did not disclose in its Bulletin to its Sales Force that its scientist who had analyzed the Milligan study had concerns about using its findings to show Duragesic’s efficacy.⁶¹⁰

298. Janssen also did not disclose in the Bulletin that the Milligan study was supported by a grant from the Janssen Research Foundation, and the lead author had received financial support from Janssen.⁶¹¹

299. In sum, in my opinion, in communicating to its Sales Force about the Milligan study regarding the use of Duragesic for chronic non-cancer pain, Janssen overstated the study’s findings on efficacy and sought to explain away negative results in the study as due to pre-

⁶⁰⁷ *Id.* at 8, 11.

⁶⁰⁸ JAN-MS-00901946.

⁶⁰⁹ *Id.*

⁶¹⁰ When Janssen proposed using the Milligan study again in Duragesic promotional materials in 2007, Vince Brett, Janssen Associate Director of Medical Communications, recommended deleting it because it was “loaded with inconsistencies, errors, and omissions of data, which calls into question the integrity of the results.” JAN-MS-00747497 at 1, 4.

⁶¹¹ JAN-MS-00311759 at 759.

existing patient characteristics, alleged improper treatment by physicians, or the fact that the study design did not include certain categories, rather than issues with Janssen's drug. These explanations were suggested by Janssen to its Sales Force even when not offered by the study's authors. Janssen also did not inform its Sales Force of the substantial increase in dosing over the study, the adverse events in the study relating to abuse/dependence and its scientists' findings and recommendations regarding them, its scientist's concerns about using the study to show efficacy, or its sponsorship of the study.

300. In a January 21, 1998 memorandum to its Field Sales Force regarding an open label study by Richard Simpson et al. published in 1997 in the *Journal of Pain and Symptom Management* entitled "Transdermal Fentanyl as Treatment for Chronic Low Back Pain,"⁶¹² Janssen advised its Sales Force that the study results suggested "that patients on DURAGESIC treated for chronic low back pain report greater improvement in pain relief and disability than those who received oral opioids," and that "use of Duragesic may be associated with less disability caused by chronic lower back pain."⁶¹³ In professional file cards and other materials used by sales representatives, Janssen likewise cited the Simpson study for its claim that Duragesic "[de]monstrated effectiveness in chronic back pain with additional patient benefits," and also claimed that "[a]ll patients who experienced overall benefit from DURAGESIC would recommend it to others with chronic low back pain."⁶¹⁴

301. In a September 2004 warning letter to Janssen regarding this file card, FDA's DDMAC found that the Simpson study was "inadequate to support th[ese] claim[s], because it

⁶¹² JAN-MS-00591572.

⁶¹³ JAN-MS-02728460 at 2. Janssen likewise did not disclose in this Sales Force memorandum that it funded the Simpson study. JAN-MS-00591572 at 572.

⁶¹⁴ JAN-MS-00299212; JAN-MS-02757939; JAN-MS-02757589.

was an open-label, single-arm trial with no control group,” and further stated “[w]e are not aware of substantial evidence or substantial clinical experience to support th[ese] claim[s].”⁶¹⁵ DDMAC found these claims to be “unsubstantiated effectiveness claims,” that they and other misleading claims on the file card were “serious” violations and constituted misbranding, and requested that Janssen “immediately cease dissemination” of the promotional file card and come up with a plan for corrective action.^{616 617}

302. In a 2002 Janssen Sales Representative Self-Study Guide, one objective of a Duragesic module was to “Explicate the Simpson study and articulate the key selling points.”⁶¹⁸ The same Guide featured another Duragesic module in which the sales representative was to describe “the causes of chronic back pain,” as well as “the etiology of degenerative joint disease” and “types of HIV/AIDS-related pain.”⁶¹⁹

303. In 1998 and 2000, FDA’s DDMAC issued additional warning letters to Janssen for promotion of Duragesic for unapproved uses.

304. On March 5, 1998, DDMAC issued a warning letter to Janssen regarding promotional posters for Duragesic that contained bold type at the top claiming that Duragesic is “recommended for use in chronic pain.”⁶²⁰ DDMAC noted, however, that the full approved indication stated that Duragesic is indicated for chronic pain “in patients who require continuous opioid analgesia for pain *that cannot be managed by lesser means*” (emphasis added), language

⁶¹⁵ JAN-MS-00779345.

⁶¹⁶ *Id.*

⁶¹⁷ Janssen responded that it disagreed with DDMAC’s position but would discontinue the file card and promotional materials with the same or similar representations. JAN-MS-00238384. Janssen also agreed to send a “Dear Doctor Letter” to physicians advising them of FDA’s warning letter. *See* JAN-MS-00191340.

⁶¹⁸ JAN-MS-00776447 at 9; JAN-MS-00776446.

⁶¹⁹ JAN-MS-00776447 at 6.

⁶²⁰ JAN-MS-00238335 at 2.

which was not included in the bold type at the top of the poster.⁶²¹ The agency found that “the presentation of the full indication near the bottom of the poster in small, inconspicuous type size” was “misleading and overwhelmed by the more prominent claim of chronic pain at the top of the poster,” and therefore determined that Janssen was promoting Duragesic “for a much broader use than that recommended in the approved product labeling.”⁶²²

305. On March 30, 2000, DDMAC issued a warning letter to Janssen regarding homemade promotional pieces for Duragesic sent to thousands of doctors which stated “It’s not just for end stage cancer anymore!”⁶²³ DDMAC found that this claim “suggests that Duragesic can be used for any kind of pain”—rather than for chronic pain in patients requiring continuous opioid treatment for pain that cannot be managed for lesser means—and thus promoted Duragesic “for a much broader use” than in the label and was misleading.⁶²⁴

306. The call notes of Janssen’s sales representatives show that into 2004 they were frequently promoting Duragesic to prescribers for lower back pain and arthritis,⁶²⁵ consistent with the marketing materials and Sales Bulletins above. Some of these call notes indicate that the sales representatives were also citing to the Milligan and Simpson studies referenced in the sales bulletins noted above in promoting Duragesic for lower back pain.⁶²⁶ For example, one Ohio call

⁶²¹ *Id.*

⁶²² *Id.*

⁶²³ JAN-MS-00238338 at 2, 7.

⁶²⁴ *Id.*

⁶²⁵ JAN-OH-00000004; JAN-OH-00000005; JAN00118956 (11 calls in 1998, 4 calls in 1999, 1 call in 2003, and 11 calls in 2004). *See also* Schedule 11.

⁶²⁶ JAN-OH-00000005.

note from April 2003 states “presented simpson study. She said they have a lot of back pain pts on short-actings atc. Asked her to recommend Duragesic to those pts.. she said yes.”⁶²⁷

307. In my opinion, Janssen’s marketing of Duragesic broadened its indications beyond the label, and thereby expanded the use of long acting opioids and contributed to the change in the practice of medicine.

3. Janssen’s Promotion of Duragesic Understated its Risk and Overstated its Benefits.

(a) Janssen Promoted Duragesic as Superior to Oral Opioids, Especially OxyContin, Without Substantial Evidence.

308. After Purdue’s OxyContin entered the market, Janssen began to promote purported advantages of the Duragesic patch over oral opioids with regards to convenience and improved functioning.

309. From late 1995 through mid-1998, Janssen’s marketing materials used the tagline “Stops the Pain Not the Patient.”⁶²⁸ Its advertisements used headlines such as “Why interrupt these moments with oral opioid dosing?” and “Between the constant pill taking and the side effects, I got exhausted just trying to control my pain,” and featured patients talking about the constipation suffered by those on “pain pills.”⁶²⁹

310. From late 1998 to late 2000, Janssen’s key tagline was “Round the Clock Living” and its advertisements used headlines such as “With pain pills, it was like punching a clock every four hours.”⁶³⁰

⁶²⁷ *Id.*

⁶²⁸ JAN-MS-00305469.

⁶²⁹ *Id.* at 5-8.

⁶³⁰ *Id.* at 5-8.

311. Starting in late 2000, Janssen's marketing tagline became "Life, Uninterrupted," with promotional materials featuring friends, couples and families being active together.⁶³¹ These materials promoted Duragesic on the basis that it offered "72 hours of uninterrupted pain relief"⁶³² and fewer peaks and troughs than oral opioids,⁶³³ and "relieve[d] the burden of taking pills 2 or more times a day."⁶³⁴ The promotions included patient quotes such as "Pain relief lasted longer with Duragesic than with the pills I was taking,"⁶³⁵ and "The patch took away the pain and let me take fewer pills."⁶³⁶

312. By this time, Janssen had begun closely tracking Purdue's sales and marketing of OxyContin. In a January 17, 2000 email, Chis Johnson, of Janssen's Sales Training Department, advised other Janssen employees, "In order for us to reach our Duragesic goals for the year 2000, we need to know as much about the competition as possible. We now have the capabilities of doing this with the Oxycontin Backgrounder. Please take the time to read through this material in its entirety..."⁶³⁷ The OxyContin Backgrounder was also distributed as part of the 2002 Janssen Sales Representative Self-Study Guide, which taught sales representatives how to "Differentiate between Duragesic and OxyContin."⁶³⁸

313. At the same time Janssen was utilizing the marketing messages above claiming Duragesic's superiority over "pain pills," Janssen explored a partnership with Purdue to co-

⁶³¹ JAN-MS-00305469 at 15.

⁶³² JAN-MS-02757939 at 2; JAN-MS-02757589 at 2; JAN-MS-02757751 at 2; JAN-MS-02757583 at 2.

⁶³³ See JAN-MS-02757939 at 2; JAN-MS-02757589 at 2; JAN00118955; JAN-OH-00000004; JAN-OH-00000005; JAN00118956; JAN-MS-02757751 at 2; JAN-MS-02757583.

⁶³⁴ JAN-MS-02757939 at 3.

⁶³⁵ *Id.*

⁶³⁶ *Id.* at 4.

⁶³⁷ JAN-MS-02727829

⁶³⁸ JAN-MS-00776447 at 8-9.

promote Duragesic and OxyContin, designated “Project Pearl.” The project looked at whether the drugs could “be positioned to physicians in a complementary way”⁶³⁹ and proposed “mirror[ing] Purdue and Janssen sales force[s].”⁶⁴⁰

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316. Although Project Pearl was apparently ultimately abandoned, Janssen continued to track OxyContin’s sales and marketing, with its focus shifting to taking market share from OxyContin. A February 2002 Duragesic Sales Force Presentation stated “Must take share from

⁶³⁹ JAN-MS-00456650.

⁶⁴⁰ JAN-MS-01051754 at 35.

⁶⁴¹ JAN-MS-02727829

⁶⁴² JAN-MS-00776447 at 8-9.

⁶⁴³ JAN-MS-00456650.

⁶⁴⁴ JAN-MS-01051754 at 35.

OxyContin” and contained multiple graphs comparing sales of the two drugs.⁶⁴⁵ The presentation noted that “despite media focus, OxyContin loses only 2.5 share points” and “Duragesic share growth has slowed, must be aggressive to meet 2002 goals.”⁶⁴⁶ It further compared sales of the two drugs among physicians in different sales deciles, revealing that while OxyContin had a larger market share than Duragesic in all deciles, the gap was largest in the highest decile prescribers. The slide with the data stated “Need to drive share in higher deciles” at top, and another slide stated “Utilize all available resources with high decile physicians.”⁶⁴⁷

317. Similarly, a May 2002 Sales Force District Meeting Presentation had a slide entitled “Beat OxyContin” with the bullet points “Sell Duragesic on every call” and “Take share from OxyContin.”⁶⁴⁸ A June 2002 Analysis of Duragesic Brand Prescribing tracked OxyContin prescribers by specialty and noted that “As the number of writers of Oxycontin has declined significantly in this Other Specialty group, it seems like Duragesic is gaining at the expense of OxyContin.”⁶⁴⁹

318. Janssen was also tracking Purdue’s sales force for OxyContin. A December 2002 email from Jay Stahl of Janssen’s Business Intelligence unit, responding to an inquiry from Chris Matteson, Associate Director of Sales Operations, provided details regarding the number of OxyContin sales representatives at different points in time and stated “Hope this helps with the

⁶⁴⁵ JAN-MS-00785983.

⁶⁴⁶ *Id.* at 8.

⁶⁴⁷ *Id.* at 12, 15.

⁶⁴⁸ JAN-MS-00246939 at 3.

⁶⁴⁹ JAN-MS-00787243 at 18.

Duragesic business plan.”⁶⁵⁰ A 2002 slide presentation compared the deployment of sales representatives and sales calls for OxyContin and Duragesic.⁶⁵¹

319. A 2003 Duragesic “Positioning/Message/Campaign--Evolution Overview” presentation provided to Janssen by KPR shows that in 2001 and 2002 KPR conducted field testing of different promotional messages for Duragesic through several surveys and other tools that compared Duragesic to OxyContin.⁶⁵² The field testing included use of the Simpson and Milligan studies mentioned above.⁶⁵³

320. The September 2003 Duragesic Brand Monitoring and Performance Enhancement Study presentation by ZS Associates contained graphs of IMS sales data showing that “Duragesic continues to gain share from OxyContin.”⁶⁵⁴ The presentation also cited results from physician surveys showing that “Duragesic is perceived to perform better than OxyContin on most attributes of high stated importance,” including “able to regain functionality.”⁶⁵⁵ The functionality message was utilized in subsequent promotional materials such as a December 2003 visual aid for pharmacists, which highlighted the claim that Duragesic provided “Chronic pain relief that supports functionality” and “improvements in physical social functioning.”⁶⁵⁶

⁶⁵⁰ JAN-MS-02990169.

⁶⁵¹ JAN-MS-00780336 at 3.

⁶⁵² JAN-MS-00306327 at 8, 9, 20, 21, 25.

⁶⁵³ JAN-MS-00306327 at 17, 19.

⁶⁵⁴ JAN-MS-00306124 at 8.

⁶⁵⁵ JAN-MS-00306124 at 8, 16.

⁶⁵⁶ JAN-MS-02757583 at 6.

(b) DDMAC Warned Janssen That its Functionality Claims and Superiority Claims Comparing Duragesic to Oral Opioids Were Misleading.

321. DDMAC issued warning letters to Janssen for various marketing materials that made superiority claims and promoted improved functioning like those above, which FDA considered to be false and misleading. In March 1998, DDMAC warned Janssen that a claim it made on a convention poster that Duragesic caused significantly less constipation than morphine was not supported by substantial evidence.⁶⁵⁷ The poster featured a statement that “[t]he constipation got so bad, I was afraid to swallow my pain pills,” accompanied by a chart comparing the incidence of constipation with Duragesic versus sustained release morphine reported in an open label study.⁶⁵⁸ FDA noted that claims of superiority to competitor drugs require substantial evidence, generally in the form of two adequate and well-controlled, head-to-head studies of the drugs. FDA did not consider the study cited to meet this standard.⁶⁵⁹

322. In fact, DDMAC found that Janssen had “selectively present[ed] the results” of the study to “provide the misleading impression that the tolerability profile of [Duragesic] is superior to sustained-release morphine.”⁶⁶⁰ DDMAC noted that Janssen “fail[ed] to present data” from the study showing that 1) subjects on Duragesic reported more sleep disturbances and shorter sleep than those on sustained release oral morphine; 2) the incidence of abdominal pain, dyspnea and sweating were “markedly higher” with Duragesic; and 3) more Duragesic subjects than morphine subjects required rescue medication.⁶⁶¹

⁶⁵⁷JAN-MS-00238335.

⁶⁵⁸*Id.*

⁶⁵⁹*Id.*

⁶⁶⁰*Id.* at 2.

⁶⁶¹*Id.*

323. In the same letter, DDMAC found similar faults with another Janssen promotional poster in which Janssen combined the statement “I needed the relief the pain pills gave me, but the constipation kept me from doing the things I wanted to do ... “ with the claim that “Duragesic provides less frequency and impact of side effects.”⁶⁶² DDMAC found that the combination of these statements “impl[ied] that Duragesic is superior to sustained-release oral morphine” without substantial supporting evidence.⁶⁶³

324. In addition, in its 1998 letter DDMAC warned Janssen that the tagline “Stops the Pain Not the Patient” was false and misleading because it implied that Duragesic was “not associated with impairment of mental or physical abilities,” even though the label contained a precaution that the use of strong opioid analgesics impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving.⁶⁶⁴

325. DDMAC concluded its 1998 letter by ordering Janssen to “immediately suspend all promotional activities and materials that convey or contain the allegedly violative claims or information identified in this letter until these allegations are resolved.”⁶⁶⁵

326. In its March 20, 2000 warning letter, DDMAC warned Janssen regarding several “homemade” promotional pieces that contained some of the same misrepresentations noted in the 1998 warning letter.⁶⁶⁶ Specifically, FDA found the claim in these materials of “Significantly LESS constipation!” to be false or misleading because it “minimize[d] the risk of constipation that is associated with Duragesic therapy” and suggested that “Duragesic is associated with

⁶⁶² *Id.*

⁶⁶³ *Id.*

⁶⁶⁴ *Id.* at 2-3.

⁶⁶⁵ *Id.* at 3.

⁶⁶⁶ JAN-MS-00238338 at 2.

significantly less constipation than other available opioids” without substantial evidence.

DDMAC referred Janssen back to its 1998 warning letter addressing the same issue.⁶⁶⁷ The March 2000 warning letter made the same findings regarding Janssen’s claim in the homemade pieces that “Duragesic results in much less Constipation compared to Oxycontin (Senokot \$1.00/day).”⁶⁶⁸

327. DDMAC also warned Janssen in its March 2000 warning letter that Janssen’s claim of “Preferred regimen: 2 x per week versus 2 x per day!” suggested that patients “prefer Duragesic to other available oral opioids that are taken twice daily” without substantial evidence, and was therefore false or misleading.⁶⁶⁹

328. Janssen was also taken to task in DDMAC’s March 2000 letter for its unsubstantiated and misleading quality of life claims that “And the #1 reason to convert your patients to the Duragesic patch: QUALITY OF LIFE,” and “...without pain, patient’s sleep better, increase daily activities, and spend more quality time with their families.”⁶⁷⁰ DDMAC noted that such “health related quality of life claims...require substantial supporting evidence in the form of adequate and well controlled studies designed to specifically assess these outcomes.”⁶⁷¹

329. Janssen continued to promote Duragesic utilizing very similar misleading claims to those above even after the 1998 and 2000 DDMAC warning letters.

⁶⁶⁷ *Id.*

⁶⁶⁸ JAN-MS-00238338 at 5.

⁶⁶⁹ JAN-MS-00238338 at 4.

⁶⁷⁰ *Id.*

⁶⁷¹ *Id.*

329.1. A March 2001 professional file card claimed that Duragesic “relieve[d] the burden of taking pills 2 or more times a day.”⁶⁷²

329.2. The same file card and a March 2002 sales aid both claimed Duragesic “significantly reduced nighttime awakenings,” citing the Simpson study.⁶⁷³

329.3. The March 2002 sales aid also claimed Duragesic provided “significant improvement in disability,” also citing Simpson, and “improvements in physical social functioning.”⁶⁷⁴

329.4. The December 2003 visual aid for pharmacists similarly claimed that Duragesic provided “Chronic pain relief that supports functionality” and “improvements in physical social functioning.”⁶⁷⁵

330. In December 2000, Janssen met with FDA to discuss a trial it planned to do to support a superiority claim that Duragesic exhibited greater patient satisfaction than OxyContin.⁶⁷⁶ Instead of an “adequate and well controlled study” of the type DDMAC had advised Janssen in its 1998 letter would be needed for such a superiority claim,⁶⁷⁷ however, Janssen proposed an open-label study, which FDA quickly rejected as inadequate to support any comparative efficacy claim.⁶⁷⁸

331. In the 2004 DDMAC warning letter discussed above in which DDMAC found that Janssen had misleadingly used the Simpson study to promote Duragesic as effective for

⁶⁷² JAN-MS-02757939 at 3.

⁶⁷³ JAN-MS-02757939 at 3; JAN-MS-02757589 at 3.

⁶⁷⁴ JAN-MS-02757939 at 3; JAN-MS-02757589 at 3.

⁶⁷⁵ JAN-MS-02757583 at 6.

⁶⁷⁶ JAN-MS-00654881.

⁶⁷⁷ JAN-MS-00238335.

⁶⁷⁸ JAN-MS-00654881.

lower back pain in a professional file card, DDMAC also warned Janssen regarding several other misleading claims similar to ones DDMAC had warned about in the prior letters above. DDMAC found that the file card made misleading claims of reduced nighttime awakenings and improvement in disability scores based upon the same study.⁶⁷⁹ DDMAC stated that “this uncontrolled study is inadequate to support such claims.”⁶⁸⁰

332. DDMAC’s 2004 warning letter also found that the file card made similarly unsubstantiated claims of improved physical and social functioning based on the Milligan study discussed above and another study.⁶⁸¹ DDMAC likewise found that these open-label studies did not support such claims.

333. Janssen’s taglines on the file card of “Work, uninterrupted,” “Life, uninterrupted” and “1,360 loaves and counting” (showing a baker at work) were found also found to be misleading by DDMAC because they implied improved social or physical functioning or improved work productivity without citing any support for these outcome claims.⁶⁸²

334. As noted above, DDMAC concluded in its 2004 warning letter by requesting that Janssen “immediately cease the dissemination of promotional materials for Duragesic the same as or similar to those described above... Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials.”⁶⁸³

⁶⁷⁹ JAN-MS-00779345 at 3-4.

⁶⁸⁰ *Id.* at 4.

⁶⁸¹ *Id.*

⁶⁸² *Id.* at 4.

⁶⁸³ *Id.* at 4.

335. While Janssen apparently did discontinue some of its promotions materials with similar messages to those DDMAC criticized in its 2004 letter,⁶⁸⁴ promotional materials with such messages had been in use by Janssen for several years, and had continued to be used even after prior DDMAC letters warned that some of the messages were misleading. Indeed, “Life, Interrupted” was Janssen’s main marketing tagline for Duragesic starting in 2000⁶⁸⁵ and was used in a number of promotional materials, including those described above.

336. Janssen also sought to keep using of the same misleading messages it had been warned about in DDMAC’s letters after 2004. In May 2005, DDMAC responded to Janssen’s request for advisory comments on a proposed Duragesic detail aid.⁶⁸⁶ DDMAC noted that the detail ad “present[ed] the claims ‘... chronic pain relief’ and ‘... chronic pain treatment...’ multiple times.”⁶⁸⁷ DDMAC found that these claims were “misleading because they imply that Duragesic is indicated for all types of chronic pain, which is inconsistent with the PI,” since the PI stated that Duragesic was indicated only for “persistent, moderate to severe pain that requires continuous, around-the-clock opioid administration for an extended period of time, and cannot be managed by other means...”⁶⁸⁸ DDMAC referred Janssen back to the communications regarding DDMAC’s March 1998 warning letter about the same issue.⁶⁸⁹

337. Call notes made by Janssen sales representatives show they frequently promoted Duragesic based on the same messages of improved quality of life and functioning, and less

⁶⁸⁴ JAN-MS-00779353.

⁶⁸⁵ JAN-MS-00305469 at 15.

⁶⁸⁶ JAN-MS-00291349.

⁶⁸⁷ *Id.* at 2.

⁶⁸⁸ *Id.* at 2.

⁶⁸⁹ *Id.* at 2.

constipation, featured in the Janssen marketing materials found to be misleading by DDMAC.⁶⁹⁰

In doing so they often invoked the same studies DDMAC found inadequate to support such claims. For example, multiple call notes from 2004 stated “discussed increased functionality with duragesic - discussed [M]illigan study results,” while another 2004 note stated “[s]howed [doctor] the Milligan study and talked about physical and social functioning with concrete examples -- left him reprint -- he seemed impressed by the data.”⁶⁹¹ An Ohio sales note from 2004 stated “[w]ent over [S]impson study, and she agreed the QOL [quality of life] would be improved with increased sleep,”⁶⁹² while one from Illinois stated “Simpson and 72 hour continuous analgeia [sic] equals improved functioning.”⁶⁹³

338. A number of the Duragesic call notes also show that Janssen made superiority claims for its drug compared to OxyContin on quality of life/functioning and side effects. Ohio call notes from 1998 stated “gave him [doctor] reasons to use dur over ms/oxy. hit on nursing home advatages. quality of life, low side effects” and “also hit m/c advantages of using pro. dur aver oxy/mscotin. quality of life.”⁶⁹⁴ Others from Ohio and elsewhere claimed Duragesic caused less constipation than OxyContin-- “dur inst of oxy less const no paek [sic] and valley”⁶⁹⁵—and allowed for better sleep.⁶⁹⁶

339. Janssen’s Business and Public Relations plans for Duragesic also show the company sought to promote the drug as improving functionality. KPR’s 2003 Duragesic

⁶⁹⁰ JAN-OH-00000004; JAN00118955; JAN00118956 (17 calls in 1998, 3 calls in 1999, and 20 calls in 2004). *See also* Schedule 12.

⁶⁹¹ JAN00118956 (see notes dated February 10, 2004 and April 16, 2004).

⁶⁹² JAN-OH-00000005 (March 19, 2004 call note).

⁶⁹³ JAN00118955 (February 16, 2004 call note).

⁶⁹⁴ JAN-OH-00000004 (September 18, 1998 call note).

⁶⁹⁵ *Id.* (November 18, 1998 call note). *See also* JAN00118956 (March 24, 2004 call note).

⁶⁹⁶ JAN00118956 (March 5, 2004 call note).

“Positioning/Message/Campaign--Evolution Overview” presentation for Janssen asserted that field testing of promotional messages for Duragesic showed that “restoration of functionality represented ‘unused airspace’ and could be adopted as an advantageous point of differentiation,” and that “restoration of functionality is a key driver and can be owned.”⁶⁹⁷

340. The 2003 Public Relations Activities PowerPoint for Duragesic referenced above identified “[l]everage functionality” as a “core brand strategy” that dovetailed with a “focus on chronic lower back pain.”⁶⁹⁸ The Public Relations presentation asserted that “[f]unctionality” is a new way for patients to understand and discuss chronic pain and treatment effectiveness with their doctors,” and suggested having functionality on unbranded websites on chronic back pain, which would also discuss Duragesic as a treatment option.⁶⁹⁹ The presentation also recommended that Janssen “enlist 3rd party groups to drive messages about functionality as the new pain measurement paradigm,” and “target pain groups” such as the American Pain Foundation, American Chronic Pain Association, and National Pain Foundation.⁷⁰⁰

341. In my opinion, Janssen misleadingly promoted Duragesic as superior to oral opioids, especially OxyContin, without substantial evidence, and overstated its functionality benefits.

⁶⁹⁷ JAN-MS-00306327 at 2, 10.

⁶⁹⁸ JAN-MS-00776219 at 3.

⁶⁹⁹ *Id.* at 18.

⁷⁰⁰ *Id.* at 24.

4. Janssen Promoted Duragesic as Having No or Lower Abuse Potential, Particularly Compared with OxyContin, Without Substantial Evidence.

342. Janssen's sales call notes show that as early as 1998, it was promoting Duragesic as having "no abuse potential" or low risk of abuse, both in absolute terms and as compared to other opioids, especially OxyContin.⁷⁰¹

343. As early as 2000, Janssen saw the abuse issue with OxyContin as creating opportunities to distinguish Duragesic and increase its market share.⁷⁰² As early as 2001, Janssen acknowledged that "abuse potential of opioids will continue to be an issue—long-term impact on market growth uncertain."⁷⁰³ Janssen was aware of increasing OxyContin abuse.⁷⁰⁴

344. Janssen business plans for 2001 through 2004 identify limited or low abuse as a Duragesic strength and potential point of differentiation, note that the impact of OxyContin abuse on Duragesic may be favorable barring class restrictions, and note that a primary driver of increased Duragesic prescribing is abuse concerns with oral opioids.⁷⁰⁵

345. Yet Janssen's marketing materials for Duragesic, like Purdue's for OxyContin, claimed that addiction to opioids was rare, and downplayed the significance of dependence. A 2001 patient booklet claimed that "addiction is relatively rare when patients take opioids appropriately," and "physical dependence is not the same as addiction and is easily managed by gradually reducing dose of the drug."⁷⁰⁶

⁷⁰¹ JAN-OH-00000004.

⁷⁰² JAN-MS-00306718.

⁷⁰³ JAN-MS-00306718 at 28.

⁷⁰⁴ JAN-MS-00246850.

⁷⁰⁵ See JAN-MS-00785798, JAN-MS-00306718, JAN-MS-00780354, and JAN-MS-00723375.

⁷⁰⁶ JAN-MS-02757826 at 22.

346. Janssen sales aids in 2002 and 2003 cited DAWN data to claim fentanyl only accounted for less than 1% of emergency visits, stating that “physicians should not let concerns of physical dependence deter them from using adequate amounts of opioids in the management of severe pain when such use is indicated.”⁷⁰⁷ By this time, however, other documents show Janssen acknowledging that the low rate of mentions in DAWN may have been due to the data only capturing emergency room admissions.⁷⁰⁸

347. In 2003, KPR conducted market research for Janssen “to assess the potential value of a DURAGESIC abuse message resulting in share increase” in light of “the attention in the popular and professional media surrounding the abuse of long-acting opioids, most prominently OxyContin.”⁷⁰⁹

347.1. The research revealed that “this is an important factor but not a key driver in the decision to prescribe a LAO [long acting opioid],” and advised that “High-volume abuse messaging will have no impact on sales of DURAGESIC and would, in fact, cast a negative shadow on the brand.”⁷¹⁰

347.2. The KPR presentation did note that “DAWN data [was] extremely well received” in certain field studies regarding Duragesic messaging,⁷¹¹ and that “Research indicates that abuse potential is important, but it should be addressed ‘separately’ from core promotional campaign.”⁷¹²

⁷⁰⁷ JAN-MS-02757589 at 7; JAN-MS-02757583 at 588.

⁷⁰⁸ JAN-MS-02757589 at 7.

⁷⁰⁹ JAN-MS-00306327 at 2.

⁷¹⁰ JAN-MS-00306327 at 2, 8.

⁷¹¹ JAN-MS-00306327 at 19.

⁷¹² JAN-MS-00306327 at 9.

348. The September 2003 Duragesic Brand Monitoring and Performance Enhancement Study presentation by ZS Associates found that “abuse potential is the main reason for decreasing OxyContin” and concomitantly that “lower abuse potential and fewer peaks and troughs are the most commonly cited reasons for increasing prescribing of Duragesic.”⁷¹³ The presentation concluded that while “lower abuse potential is the leading reason for increased Duragesic use” and “efforts to foster awareness of abuse issues may help accelerate and maintain the shift to Duragesic,” such efforts “must be carefully designed to minimize negative effects on the class as a whole.”⁷¹⁴

349. Over the same time period, Janssen was receiving a substantial number of abuse or addiction related adverse event reports for Duragesic. For each of the three consecutive years from April 2000 until April 2003, between 134 and 155 such reports were reported by Janssen in its Periodic Safety Update Reports, with those annual totals including between 20 and 55 cases where the abuse resulted in death.⁷¹⁵

350. The tension between, on the one hand, Janssen’s internal acknowledgement of abuse of Duragesic and the lack of data to support its lower abuse claims, and on the other, its continued promotion of the drug as less abuse prone than OxyContin, showed in a February 2000 discussion of Janssen’s “OxyContin Backgrounder” sales training aid. In response to the prompt “Give an advantage of Duragesic over Oxycontin as it relates to addiction?,” the Backgrounder

⁷¹³ JAN-MS-00306124 at 12, 13.

⁷¹⁴ JAN-MS-00306124 at 39.

⁷¹⁵ JAN-MS-02338206 at 50 (PSUR for April 2000 to April 2001, showing 155 cases of abuse or addiction, including 50 which resulted in death); JAN-MS-00911743 at 13, 43 (PSUR for April 2001 to April 2002, showing 144 cases of abuse or addiction, including 20 which resulted in death); JAN00221849 at 48-49 (PSUR for April 2002 to April 2003, showing 134 cases of abuse or addiction, including 55 which resulted in death).

states “Potentially, less street value, toxic when crushed,” but then notes “Consider rewording this question, Duragesic can be chewed.”⁷¹⁶

351. Janssen also acknowledged the lack of data supporting its lower abuse claims in a memorandum reporting on an August 14, 2001 meeting to discuss an upcoming FDA advisory board regarding OxyContin abuse issues. The memorandum listed objectives for the FDA meeting, including “to help protect the class from restrictive actions that would further hinder proper patient care, or in a sense defend the class.”⁷¹⁷ In response to another objective, “To actively differentiate Duragesic from oral formulations and Oxycontin, and position ourselves as an alternative with potentially less abuse potential,” Pamela Rasmussen inserted “I think there’s another option: Advocate for aggressive treatment of pain, defend the class and ‘mention’ that there are multiple types and formulations of opioids, which have different safety/benefit profiles -- including the product that has shaped our own involvement in the field, Duragesic....The Key is not to turn this into a promotional platform (especially since I don’t think we have enough data to back up our less abuse claim).”⁷¹⁸

352. A similar recognition of lack of support for its lower abuse claim is seen in the company’s November 30, 2001 Executive Summary for Chronic Pain Scientific Advisory Board, which discussed messages relating to the abuse potential of Duragesic, including “DURAGESIC provides pain relief in sustained-release transdermal formulation and has a reported rate of abuse between 0 and 0.1%.”⁷¹⁹ However, the Summary noted in regards to this message the “Continued rejection of the DAWN data and abuse statistics,” and acknowledged a lack of knowledge and

⁷¹⁶ JAN-MS-02727830 at 2.

⁷¹⁷ JAN-MS-00899138 at 2.

⁷¹⁸ JAN-MS-00899137; JAN-MS-00899138 at 2.

⁷¹⁹ JAN-MS-00782617 at 7.

data about the abuse potential for Duragesic patients with no history of substance abuse.⁷²⁰ The Summary made the “Conclusion: Do not include the abuse message. Do not sell opioids on the abuse issue.”⁷²¹

353. Yet Janssen continued to promote Duragesic as having a lower risk of abuse than OxyContin. Sales training materials from August 2001 provide examples of how Duragesic sales representatives could respond to doctors raising abuse related to OxyContin, including the statement that “due to the technology of the patch delivery system many pain specialists believe that Duragesic has less potential for abuse.”⁷²²

354. In 2002 Janssen provided a \$50,000 grant to the American Pain Foundation for a patient education brochure which stated that “there is little risk of addiction” with opioids when taken as properly prescribed and directed, “unless you have a history of substance abuse.”⁷²³ The brochure also stated that “physical dependence—which is not addiction...” usually is not a problem if you go off your medications gradually.”⁷²⁴

355. In its March 2000 warning letter discussed above, DDMAC also found that Janssen’s claim of “Low abuse potential!” in the homemade piece at issue was false or misleading because it suggested that “Duragesic has less potential for abuse than other currently available opioids” without substantial evidence.⁷²⁵ DDMAC further noted that “this claim is contradictory to information in the approved product labeling (PI) that states, ‘Fentanyl is a

⁷²⁰ *Id.*

⁷²¹ *Id.*

⁷²² JAN-MS-00313051 at 2.

⁷²³ JAN-MS-00723779; JAN-MS-00788087; ABT-MDL-KY-0025968. The company described this grant internally as “a verbal commitment; nothing was put in writing.” JAN-MS-00723779.

⁷²⁴ ABT-MDL-KY-0025968 at 3.

⁷²⁵ JAN-MS-00238338 at 2.

Schedule II controlled substance and can produce drug dependence similar to that produced by morphine.”⁷²⁶ DDMAC also found that Janssen failed to present any risk information concerning warnings, precautions, side effects or contraindications, and thus the piece was “lacking in fair balance.”⁷²⁷

356. In its 2004 warning letter regarding a Janssen professional file card described above, DDMAC also found that the file card made unsubstantiated claims of lower abuse than other opioids. DDMAC found that relying on the reported rate of mentions in DAWN data was misleading because Duragesic was not as widely prescribed as other drugs.⁷²⁸

357. The DDMAC letter prompted Janssen executive Scott Reines to write Janssen VPs regarding the letter, stating, “not as egregious as the Risperdal situation, but there is plenty of evidence that our promotional material is not being adequately self-regulated.”⁷²⁹

358. An April 2006 letter to Janssen from FDA commented on Janssen’s Duragesic risk management plan and requested that Janssen “provide the definition and criteria used to identify adverse event reports related to addiction, as well as a list of adverse event terms that are coded under the term ‘addiction,’” “list adverse event terms that are coded under ‘misuse’ and ‘abuse,’” and “emphatically state that Duragesic should not be used in opioid naïve patients.”⁷³⁰

359. FDA’s letter prompted Janssen Therapeutic Area Manager Dawn Sanderson-Bongiovanni, PharmD, to write Dr. Bruce Moskovitz, Janssen Therapeutic Area Head for Analgesia & GI. Dr. Sanderson-Bongiovanni noted that she was researching concerns raised by

⁷²⁶ *Id.* at 2.

⁷²⁷ JAN-MS-00238338 at 4.

⁷²⁸ JAN-MS-00779345.

⁷²⁹ JAN-MS-02478753.

⁷³⁰ JAN-MS-00480894 at 1-2.

FDA in its response to Janssen's Duragesic RiskMap proposal, and asked if Dr. Moskowitz could "site [sic] a 'landmark' article that reflects current medical thinking about the occurrence and etiology of addiction (induced by opioid therapy)?"⁷³¹

360. Dr. Moskowitz forwarded the request to Dr. Vorsanger and Dr. David Hewitt, a neurologist in the analgesia group, stating "pain and addiction are not my specialty."⁷³² Dr. Hewitt responded that "*the evidence supporting the low abuse potential among patients receiving opioids for chronic pain is not based upon strong data. Margo McCaffery discusses <1%. I have seen numbers that suggest the rate of addiction is similar to the population at large and no higher.*"⁷³³

361. Dr. Vorsanger responded to Dr. Hewitt, "I am skeptical of the low rates that Margo and others cite. Remember, rates of addiction for non-opioid substances such as alcohol are much higher (rates of 5-8% or even higher have been quoted for the general population)."⁷³⁴ In his deposition, Dr. Moskowitz agreed, testifying that studies on iatrogenic addition with chronic pain patients provide "a potentially inaccurate estimate, it may underestimate the rate of abuse, misuse, and diversion. And particularly addiction and those reports of addiction."⁷³⁵

362. In the period prior to the exchange above between Janssen clinical executives and the introduction of the first generic version of Duragesic in early 2005, Janssen reported over 300 annual adverse events involving abuse or addiction with the drug for April 2003 to April 2004,⁷³⁶

⁷³¹ JAN-MS-00957863 at 2.

⁷³² JAN-MS-00957863 at 1.

⁷³³ *Id.* (emphasis added).

⁷³⁴ *Id.*

⁷³⁵ Moskowitz Dep. 695:2-700:21, November 14, 2018 (testifying regarding the exchange between himself, Dr. Vorsanger, Dr. Hewitt, and Dr. Sanderson-Bongiovanni in JAN-MS-00957863).

⁷³⁶ JAN00221868 at 128.

and over 400 for April 2004 to April 2005⁷³⁷. In the latter period the adverse events included 76 which resulted in death.⁷³⁸

363. Janssen's sales call notes indicate that it was frequently promoting Duragesic on the basis that DAWN data showed it had low abuse rates.⁷³⁹ For example, a April 21, 2004 call note stated "Showed him the DAWN data and how Dur[agesic] is very low abuse potential"⁷⁴⁰ and an August 11, 2004 note stated "...thought that dur[agesic] was highly abusable. Presented DAWN data for low abuse potential."⁷⁴¹

364. Sales call notes also show that Janssen marketed Duragesic to nursing home residents from 1998 on the basis of low abuse potential, quality of life and convenience.⁷⁴²

365. In my opinion, Janssen misleadingly promoted Duragesic as having no or lower abuse potential, particularly compared with OxyContin, without substantial evidence.

5. Janssen Made Shifting and Unsubstantiated Claims Regarding the Abuse Potential of the Reservoir v. Matrix Formulations of Duragesic as the Sales Environment for the Drug Shifted.

366. Janssen's Duragesic system approved in the United States in 1990 was a "reservoir" patch system that "utilized a form-fill-seal design: a drug reservoir of fentanyl and alcohol gelled with hydroxyethyl cellulose that delivers fentanyl to the skin across a rate-controlling membrane."⁷⁴³

⁷³⁷ JAN-MS-00553427 at 138.

⁷³⁸ JAN-MS-00553427 at 22.

⁷³⁹ See JAN-OH-00000005, JAN00118955.

⁷⁴⁰ JAN00118956.

⁷⁴¹ JAN00118955.

⁷⁴² JAN-OH-00000004.

⁷⁴³ Jan-MS-00386726 at 3.

367. From 1993 through 2004, Janssen's sales of Duragesic totaled over \$6 billion.⁷⁴⁴

368. In November 2003, FDA approved a generic version of the Duragesic patch made by Mylan that used a different design called matrix.⁷⁴⁵ Matrix-designed products consist of an entirely solid material in which fentanyl is embedded in a layer of adhesive.⁷⁴⁶ Janssen's sales dropped from a high of over \$1 billion in 2004 to over \$600 million in 2005, the first year the Mylan generic patch was sold, and dropped further to just under \$400 million in 2006.⁷⁴⁷

369. In 2001, Janssen had considered moving from its Duragesic reservoir to a matrix formulation (then referred to by Janssen as "D-TRANS"),⁷⁴⁸ and had commissioned a report from Pinney Associates entitled "D-TRANS Fentanyl: Summary of Benefits and Risks: Abuse and Diversion."⁷⁴⁹ The Pinney report noted that potential "areas of vulnerability" of the new matrix formulation included that it "contains theoretically higher amounts of divertible drug compared to the existing formulation" and "is potentially subject to extraction approaches that would be considered acceptable to drug abusers and illicit drug distributors."⁷⁵⁰

370. The Pinney report concluded that while the matrix formulation was "approvable," the fact that it "will contain substantially more potentially abusable fentanyl in both the unused and used systems," and the environment of heightened regulatory scrutiny, "will almost certainly lead to a very critical review which could lead to significant threats to approval, limitations on

⁷⁴⁴ PPLP003364349.

⁷⁴⁵ FDA letter to Mylan Technologies, June 22, 2004, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2004/76-258 rescind.ltr.pdf (last visited March 20, 2019).

⁷⁴⁶ JAN-MS-00386726 at 3.

⁷⁴⁷ PPLP003364349.

⁷⁴⁸ Moskowitz Dep. 160:15-24, November 13, 2018.

⁷⁴⁹ JAN-MS-02119824.

⁷⁵⁰ *Id.* at 6.

marketing, and stronger misuse/abuse ‘detering’ labeling.”⁷⁵¹ Janssen did not seek approval of a matrix formulation at that time.

371. While sales of the generic Mylan matrix product approved in 2003 were delayed until early 2005 due to patent litigation,⁷⁵² Janssen set in motion plans to counter competition from it in the meantime. A Duragesic Business Update from January 2004 concerned selecting a “viable strategy to protect current asset: protect against AB [generic equivalency] rating”⁷⁵³ and meeting an objective to “establish differentiation between reservoir and matrix technology in a timely manner (AB rating).”⁷⁵⁴

372. The “optimal strategy” identified in the 2004 Business Update was “different dosage forms,” for which “key tactics” included conducting abuse liability studies to show “ease of extraction” and “attractiveness (from abuser’s perspective)” of matrix compared to reservoir, and filing a Citizen’s Petition with the FDA.⁷⁵⁵

373. In a section entitled “Defend Current Asset,” the Business Update included advertisements with the tagline “Confidence, Interrupted”—a play on Duragesic’s existing tagline of “Life, Interrupted.”⁷⁵⁶ These ads questioned whether matrix was a true generic equivalent, despite FDA’s approval of it as such, and contained comparative abuse liability claims such as “The Matrix Fentanyl Deliver System is an attractive target for diversion,” “The Matrix Fentanyl Deliver System: Why Take the Chance of Abuse and Diversion?,” and “The

⁷⁵¹ *Id.* at 5, 7.

⁷⁵² FDA letter to Mylan Technologies, June 22, 2004, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2004/76-258 rescind.ltr.pdf (last visited March 20, 2019)

⁷⁵³ JAN-MS-02396626 at 2.

⁷⁵⁴ *Id.* at 10. At the same time, Janssen explored options for partnering “with a generic company to retain as much of the Fentanyl reservoir market share as possible.” *Id.* at 32, 34.

⁷⁵⁵ *Id.* at 12, 24, 72.

⁷⁵⁶ *Id.* at 62-66.

Matrix Fentanyl Deliver System: A Threat to Patient and Public Safety?”⁷⁵⁷ Another ad in the Update claimed that matrix “encourages drug-seeking behavior.”⁷⁵⁸ The ads further raised the specter of “increased liability of health care providers” and suggested that prescribing Duragesic could avoid same.⁷⁵⁹

374. Also in January 2004, Janssen developed a script and materials for its sales force to use in persuading physicians to prescribe its reservoir Duragesic patch over the generic matrix patch.⁷⁶⁰ Like the ads in the Business Update, these promotional materials emphasized a claimed greater risk of misuse and abuse with matrix than with Duragesic. For example, the script claimed that “the differences between the matrix and the DURAGESIC reservoir can put your patients and the public at risk,” and that matrix “falls far short of the high public safety standard of DURAGESIC.”⁷⁶¹ It asserted that with matrix fentanyl could “be easily extracted from the patch by chewing, soaking, or other means-thus creating the potential for a real public safety problem” and that “matrix can also be cut into smaller pieces-another risk to public safety.”⁷⁶²

375. The script invoked DAWN data to claim that “Duragesic is not attractive to abusers,” and asserted that Duragesic had “an extremely low rate of abuse.”⁷⁶³ As noted above, by this time Janssen had been warned by DDMAC about misleading marketing claims regarding

⁷⁵⁷ *Id.* at 30-31, 62-66.

⁷⁵⁸ *Id.* at slide 31.

⁷⁵⁹ *Id.* at slide 31, 64, 66; The Business Plan Update also shows that Janssen planned to continue “‘aggressive’ sales force promotion through 2004” with “high-frequency” calls to current Duragesic prescribers and “high-volume pharmacies,” and to “align incentive compensation” to “minimize erosion.” *Id.* at 27. A March 2004 “Duragesic Contingency Plan Update” similarly shows Janssen planned to “focus on high-volume MDs and pharmacists” and “target top Duragesic writers” for sales calls prior to the launch of Mylan’s generic matrix. JAN-MS-02990985 at 13, 17.

⁷⁶⁰ JAN-MS-00724843.

⁷⁶¹ *Id.* at 1, 4.

⁷⁶² *Id.* at 2.

⁷⁶³ *Id.* at 7.

Duragesic's low abuse potential, and was aware of DAWN's limits in accurately measuring abuse. Also as noted above, by this time Janssen had reported in its PSURs for Duragesic over 544 cases involving drug abuse or addiction, over 125 of which resulted in death.

376. The script further claimed that reservoir Duragesic would “protect[] you and your liability in prescribing.”⁷⁶⁴ It went on to assert that each matrix patch could cause an abuse epidemic and harm patients with chronic pain by limiting their access to medication:

So if the wrong person gets their hands on one of these new matrix systems, they are looking at the equivalent of between 100 and 200 tablets of oxycodone. If they get a whole box, just think of how much more that is. *And how many people that could affect.* As we've seen with oxycodone, this is exactly what abusers are looking for—a delivery system that both contains a lot of drug and can be easily defeated to get a quick high. Each one of these little matrix systems contains all the potential for another epidemic—which means another crisis not only for the public, but for prescribers as well. Furthermore, it could negatively impact patients with chronic pain by limiting access to the effective pain therapy they legitimately need.⁷⁶⁵

377. The script concluded that “this new ‘generic’ matrix system isn't really a generic at all—it is a completely different system, and one that could pose a great threat to you, your patients, and the public at large” and that these risks could be avoided by prescribing Duragesic instead.⁷⁶⁶

378. Yet, Janssen itself launched a fentanyl matrix patch in Europe in 2004, called D-Trans, the same year it prepared the Business Update and script above.⁷⁶⁷ In 2003, in preparation for this launch, Janssen had prepared an “assessment of the potential for prescription analgesic

⁷⁶⁴ *Id.* at 3.

⁷⁶⁵ *Id.* at 5-6 (emphasis in original).

⁷⁶⁶ *Id.* at 8; Janssen's testing of the messages contained in the ads and sales script indicated they made doctors more likely to increase prescriptions of Duragesic and to “attempt to ensure that patients received the Duragesic brand,” based in part on “the potential difference in abuse potential.” JAN-MS-02391035 at 47-50. Janssen projected a positive ROI [return on investment] of \$100-150 million in 2005 as a result. *Id.* at 50.

⁷⁶⁷ JAN-MS-02135033 at 2.

abuse, misuse and diversion in Europe.”⁷⁶⁸ Janssen reported that the abuse expert consulted for the assessment opined that “there is no evidence that prescribed opioids are abused to a significant extent” and “fentanyl is not an attractive compound for drug addicts.”⁷⁶⁹ Contrary to Janssen’s dire warnings in the documents above, the expert found it “highly unlikely” in the European context that the matrix system would “trigger more significant diversion” than the existing reservoir system.⁷⁷⁰

379. While Janssen would later reverse itself and adopt the position of its European expert as to the United States also, *see infra*, in June 2004, shortly after its matrix was approved in Europe, it received a draft of an update it had commissioned of the 2001 Pinney report discussed above, entitled “Assessment of Abuse Potential of the Matrix Formulation of Fentanyl Transdermal System: Update of the 2001 Pinney Associates’ Report.”⁷⁷¹ Echoing the promotional messages in the sales script and ads above, the assessment found that “availability of a matrix formulation ... would be expected to increase the rates of abuse because of the ability to more easily abuse and/or divert drug by cutting a matrix ... into smaller unit doses or extracting it from the matrix technology,” and “might fuel” new types of abuse.⁷⁷² It further noted that “it is plausible that US regulatory agencies would have appropriately greater concerns than their colleagues in many other countries in Europe...”⁷⁷³

380. The assessment concluded that “a matrix [fentanyl patch] should not, and more likely cannot, be marketed without a strong RiskMAP that provides evidence-based elements or

⁷⁶⁸ JAN-MS-01200052.

⁷⁶⁹ *Id.* at 7.

⁷⁷⁰ *Id.* at 8.

⁷⁷¹ JAN-MS-02119824.

⁷⁷² *Id.* at 38.

⁷⁷³ *Id.* at 4.

tools to minimize abuse and diversion and enable rapid detection of abuse and diversion that would occur.”⁷⁷⁴

381. A few months earlier, in February 2004, Dr. Moskovitz wrote to an executive at Mudskipper Strategies regarding abuse studies Janssen was “embarking on” to “differentiate Duragesic (reservoir) from the ‘unprotected’ matrix patch.”⁷⁷⁵ Dr. Moskovitz explained to the Mudskipper executive that Janssen had identified a series of such studies a year prior for comparing AP-48, Janssen’s planned new version of Duragesic with naltrexone, to generic matrix, but that since AP-48 was “delayed significantly” the focus was now on comparing the reservoir Duragesic on the market to matrix instead.⁷⁷⁶ Dr. Moskovitz noted that he anticipated that a “white paper” based on the studies would be used to “‘paint’ a full picture of risks associated with the matrix patch.”⁷⁷⁷ As noted above, abuse liability studies were identified as a “key tactic” to differentiate matrix from Duragesic reservoir for marketing purposes in the 2004 Business Update.⁷⁷⁸

382. In September 2004, a few months after receiving the Pinney Associates Assessment described above, Dr. Moskovitz gave an internal presentation on comparative abuse liability studies Janssen had conducted of reservoir and matrix.⁷⁷⁹ His conclusions and recommendations based upon those studies were closely similar to those in the Pinney Associates Assessment, and included “Fentanyl matrix patches may increase safety risk in real-

⁷⁷⁴ *Id.* at 38.

⁷⁷⁵ JAN-MS-01196462. Mudskipper “acted for [Janssen] in collating all of the information that [Janssen] collected over the course of 2003-2004 relative to...questions about the relative benefits and risks of the Duragesic reservoir or matrix.” Moskovitz Dep. 162:3-17, November 13, 2018.

⁷⁷⁶ *Id.*

⁷⁷⁷ *Id.*

⁷⁷⁸ JAN-MS-02396626 at 12.

⁷⁷⁹ JAN-MS-00478361.

world usage,” “Fentanyl matrix patches may present increased societal risk,” and “Stringent risk management programs should be mandatory for fentanyl matrix patches.”⁷⁸⁰

383. Later that month Dr. Moskovitz wrote to other Janssen executives regarding the studies:

We believe the FDA will consider these studies supportive of our position that the reservoir patch and matrix patch should be considered two different formulations and, therefore, not be A/B rated (interchangeable at the pharmacy). This lack of interchangeability would have a huge impact in the market... The data will also be of significant interest to healthcare providers and inform them of the potential risks for not writing Do Not Substitute.”⁷⁸¹

384. Dr. Moskovitz additionally stated in his email, “We believe the data will lead many HCPs to prescribe Duragesic with instructions Not to Substitute.”⁷⁸²

385. The “white paper” prepared for Janssen by Mudskipper Strategies regarding the abuse studies, anticipated by Dr. Moskovitz’s February 2004 email, arrived September 22, 2004.⁷⁸³ Again echoing the marketing messages described above, it found that “Fentanyl matrix patches are more attractive to potential abusers than DURAGESIC® reservoir patches,” that “availability of a fentanyl matrix patch is likely to increase the diversion of patches with major public health consequences,” and that “the abuse potential for a fentanyl matrix patch is significantly higher than that of the DURAGESIC® reservoir patch.”⁷⁸⁴

386. The white paper’s conclusions also included “manufacturers of fentanyl matrix patches should be required to implement stringent and comprehensive risk management surveillance and intervention programs for their products,” “Given the substantial differences in

⁷⁸⁰ *Id.* at slides 43, 44.

⁷⁸¹ JAN-MS-00482680 at 3.

⁷⁸² *Id.* at 1.

⁷⁸³ JAN-MS-00617066.

⁷⁸⁴ *Id.* at 84-85.

risks for abuse and misuse...the DURAGESIC reservoir patch and fentanyl matrix patches should not be considered interchangeable,”⁷⁸⁵ and “Fentanyl matrix patches present an unacceptable additional risk both to patient safety and public health in the U.S.”⁷⁸⁶

387. On November 12, 2004, Janssen, through Alza, filed a Citizen’s Petition with the FDA that made the same arguments as in the white paper it commissioned. Janssen’s Petition requested that the FDA take action against manufacturers of fentanyl matrix delivery systems to “reduce the potential for abuse of certain types of these products.”⁷⁸⁷ Specifically, the Petition urged FDA to: 1) “require manufacturers of fentanyl matrix systems to develop and implement comprehensive risk minimization programs that successfully address the specific issues presented by their products” and 2) “classify matrix and reservoir fentanyl transdermal systems as different dosage forms...that are not pharmaceutical equivalents.”⁷⁸⁸ The latter action would mean reversing FDA’s decision to give Mylan’s generic matrix patch an AB-rating, an action which Dr. Moskovitz had previously stated “would have a huge impact in the market,” as noted above.

388. Janssen argued these actions were called for because “(1) matrix systems can be cut into small pieces, and (2) fentanyl is more easily extracted under certain conditions from a matrix product than from a reservoir system, matrix systems present a different and possibly larger potential for abuse in the United States compared to the Duragesic® reservoir system,”

⁷⁸⁵ *Id.* at 84-85.

⁷⁸⁶ *Id.* at 12.

⁷⁸⁷ JAN-MS-00386726.

⁷⁸⁸ *Id.*

citing as support one of the abuse studies it had commissioned earlier in the year to differentiate reservoir from matrix.⁷⁸⁹

389. FDA rejected Janssen's Citizen Petition on January 28, 2005.⁷⁹⁰ FDA found that reservoir and matrix were pharmaceutically equivalent under its rules and past practices.⁷⁹¹ As to Janssen's argument that matrix would be more prone to abuse, FDA stated, "we believe that both the reservoir and matrix fentanyl transdermal systems have the potential to be abused, and petitioners have not presented data sufficient to persuade us that matrix products have a greater abuse liability potential than reservoir ones. We find that theoretical differences in potential abuse liability are not sufficient to reclassify [matrix]."⁷⁹²

390. In addition, FDA found the abuse study Janssen submitted to be "flawed because... 'the researchers note that nearly a quarter of [persons sampled] claimed experience with the fentanyl matrix patch, which was not available.'"⁷⁹³ FDA also noted that the "statistical validity of the "Opioid Attractiveness Scale" and of the sample size used for [Janssen's] study has not been demonstrated."⁷⁹⁴

⁷⁸⁹ *Id.* at 2, 5. Janssen cast the fact that it was itself marketing matrix in Europe as a source of credibility, instead of as an inconsistency, and argued that "the environment regarding prescription drug abuse in Europe differs from that in the US." *Id.* at 7, n.6). However, Janssen formulated messages to use in response to European inquiries regarding its attempt to block an equivalent matrix product in the U.S. partly on the grounds of it being more prone to abuse. JAN-MS-00891010.

⁷⁹⁰ JAN-MS-00950449.

⁷⁹¹ *Id.* at 3-4.

⁷⁹² *Id.* at 6.

⁷⁹³ *Id.* at 7.

⁷⁹⁴ *Id.* at 7.

391. FDA granted final approval to Mylan's generic matrix patch on February 2, 2005.⁷⁹⁵

392. In early 2008, FDA required that Janssen issue a recall of its Duragesic patches due to manufacturing issues.⁷⁹⁶ In January 2008, Ravi Desiraju, Janssen's Clinical Director and Team Leader for Duragesic, wrote to Dr. Moskowitz, asking, "with these problems with the reservoir patches (cut patches, fold-overs) will we be better off with matrix patches?"⁷⁹⁷ A discussion over email ensued between Desiraju, Dr. Moskowitz, and Scott Trembley, Product Director-Established Products, about whether there was more diversion with matrix than reservoir, and whether obtaining matrix approval would involve delays.⁷⁹⁸ Trembley raised reviving the AP-48 (Naltrexone matrix) program as an alternative, to which Desiraju responded that AP-48 was terminated due to negative outcomes in a pivotal clinical study, and he was "raising the reservoir/Matrix issue in light of the manufacturing problems we are currently having."⁷⁹⁹

393. On March 11, 2008, Desiraju reported to Steven Silber, Vice President – Established Products, on Janssen's consideration of developing a matrix patch, noting that Janssen had filed a Citizen Petition requesting FDA not approve generic matrix a few years earlier.⁸⁰⁰ Desiraju wrote, "In light of this history, the team felt that we should first investigate if the rate of abuse with the matrix formulation is any higher than the reservoir product," and that

⁷⁹⁵ FDA Clears Generic Version of Pain Patch (February 2, 2005). available at <https://www.webmd.com/pain-management/news/20050202/fda-clears-generic-version-of-pain-patch-news> (last visited March 20, 2019)

⁷⁹⁶ JAN-MS-00747681.

⁷⁹⁷ JAN-MS-02007690 at 3.

⁷⁹⁸ *Id.*

⁷⁹⁹ *Id.* at 1.

⁸⁰⁰ JAN-MS-00351356.

Dr. Moskowitz had therefore contacted Rick Dart of the RADARS surveillance group, who advised that “both reservoir and matrix are abused to a similar extent” and “he is not aware of any differences between the two,” though “his surveillance program is not sensitive enough to pick up any differences....”⁸⁰¹

394. On March 21, 2008, Janssen had a teleconference with FDA regarding recent recalls of its Duragesic patches.⁸⁰² As Dr. Moskowitz summarized in a March 23, 2008, email to other Janssen executives, “FDA made clear they would not allow for another recall of the type we had in 2004 and earlier this year. They indicated they would urge we move to an alternative formulation (matrix being the only viable option at the moment), but were open to learning more about our decisions in 2000 and 2004 to remain with the reservoir and review data we will submit for abuse and diversion of the reservoir and matrix. While we may ultimately decide to proceed with development of a matrix formulation for the US, we must proceed with an open mind to evaluate the data for risks of abuse and diversion, as well as risks for patient exposure from a manufacturing defect.”⁸⁰³

395. On April 24, 2008, a RADARS report for Janssen found that “RADARS System data indicate that all patch formulations show evidence of abuse, misuse and diversion.”⁸⁰⁴ Dr. Moskowitz forwarded it to Desiraju the next day in an email that backtracked on his earlier research, showing that Janssen had come full circle on matrix since vigorously opposing its approval on safety grounds in 2004.⁸⁰⁵ Dr. Moskowitz’s email stated that based upon the

⁸⁰¹ *Id.*

⁸⁰² JAN-MS-02005184.

⁸⁰³ *Id.*

⁸⁰⁴ JAN-MS-01200481.

⁸⁰⁵ JAN-MS-01200479.

RADRARS data he had concluded that “there is insufficient evidence...to suggest that levels of abuse and diversion of the matrix...patches are substantially higher than those for reservoir patches, and that lacking such data, J&J feels comfortable that we would not be increasing risks to patients if we develop a matrix patch.”⁸⁰⁶

396. Janssen followed through by submitting an NDA for approval of a Duragesic matrix formulation in the U.S. on January 30, 2009.⁸⁰⁷ The marketing plan Janssen submitted to FDA in March, 2009 indicated that it would cease shipping Duragesic reservoir patches once the matrix patch was approved.⁸⁰⁸ Final approval was granted on July 31, 2009.⁸⁰⁹

397. A Janssen “Media Messages” primer regarding the transition from reservoir to matrix, dated April 21, 2009 and labeled for “reactive use only,” explained that the change was happening because “After several years of making both a reservoir and a matrix patch globally, and after continued surveillance, the company determined that our initial concerns about risk of abuse of the matrix-style patch in the United States have not materialized.”⁸¹⁰

398. In response to questions regarding why Janssen had changed its position on matrix since its 2004 Citizen Position, the Media Messages primer instructed to respond, “At that time we were concerned about possible risks of diversion and abuse in the United States with the matrix-style patch. Since then, active surveillance of current safety data shows no abnormally

⁸⁰⁶ *Id.*

⁸⁰⁷ JAN-MS-04230555.

⁸⁰⁸ JAN-MS-00885848.

⁸⁰⁹ JAN-MS-00292753.

⁸¹⁰ JAN-MS-01250151 at 2.

high level of abuse or diversion in the United States for currently marketed fentanyl matrix systems.”⁸¹¹

399. On December 1, 2009, four months after Duragesic matrix was approved, FDA advised Janssen that “there were growing concerns within the agency regarding the residual content in the DURAGESIC matrix patch--70% more residual fentanyl in the matrix patch compared to reservoir,” and that its concerns “were related to potential misuse, abuse, disposal and exposure into the water.”⁸¹² FDA requested that Janssen “consider developing a new Duragesic patch formulation to minimize the residual fentanyl,” and stated...“We know that it is technically feasible.”⁸¹³

400. Janssen responded to FDA that it would conduct feasibility studies “to determine if we can lower the fentanyl amount using the current Duragesic Matrix formulation.”⁸¹⁴ Janssen conducted such studies and advised FDA in 2016 that it would be seeking supplemental approval for a reformulated matrix with reduced residual fentanyl, but that it “does not have data to demonstrate that the new formulation with lower residual content would decrease the risk of abuse, addiction, or life-threatening/fatal outcomes in case of accidental exposure.”⁸¹⁵

401. In my opinion, Janssen made misleading, unsubstantiated and shifting claims regarding the abuse potential of the reservoir v. matrix formulations of Duragesic as the sales and regulatory environment changed.

⁸¹¹ *Id.* at 3. In August 2009, Lori Lonczak, head of Marketing, Pain Franchise, asked Scott Trembley, Marketing/Commercial Leader for Duragesic, to send a voicemail to sales representatives about the formulation change. JAN-MS-00280657. Trembley noted “I would STRONGLY encourage no proactive communication by the field...” in part because “it could create a question as to our 2004 position on a matrix vs. today. A key Duragesic prescriber could surface all the issues above.” *Id.* at 2.

⁸¹² JAN-MS-02410536.

⁸¹³ *Id.*

⁸¹⁴ JAN-MS-00888210.

⁸¹⁵ JAN-MS-00587189 at 7, 13.

402. In my opinion, Janssen's promotion of Duragesic understated its risks and overstated its benefits, and was false and misleading.

C. Nucynta

403. Nucynta is the brand name for tapentadol, an opioid analgesic marketed by Janssen, a Johnson & Johnson company, from 2009 until 2015.⁸¹⁶

404. Tapentadol's exact mechanism of action is unknown, but it is believed to derive from its mu-opioid agonist activity and inhibition of norepinephrine reuptake.⁸¹⁷

405. Nucynta was first approved by FDA in immediate-release form as Nucynta IR in November, 2008,⁸¹⁸ for relief of moderate to severe acute pain in patients 18 years of age or older.⁸¹⁹ Sales began in June 2009.⁸²⁰

406. An extended-release form, Nucynta ER, was approved by FDA in August, 2011,⁸²¹ for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.⁸²²

407. In August, 2012, neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults was added to the indication for Nucynta ER, also for when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.⁸²³

⁸¹⁶ In this report, "Janssen" refers to all Johnson & Johnson companies and their predecessors, successors and affiliates involved in the manufacturing, marketing and promotion, and sale of Nucynta IR and Nucynta ER, including Defendants Janssen Pharmaceutica, Inc. N/K/A Janssen Pharmaceuticals, Inc.; Janssen Pharmaceuticals, Inc.; Johnson & Johnson; and Ortho-McNeil- Janssen Pharmaceuticals, Inc. N/K/A Janssen Pharmaceuticals, Inc., as well as Alza Corporation and Pricara.

⁸¹⁷ Nucynta IR label, November, 2008, JAN-MS-00445032; Nucynta ER label, August, 2011, JAN-MS-02544901.

⁸¹⁸ JAN-MS-01130740

⁸¹⁹ Nucynta IR label, November, 2008, JAN-MS-00445032

⁸²⁰ JAN-0014-0021012

⁸²¹ Nucynta ER Approval letter, August 25, 2011, JAN-MS-00214315

⁸²² Nucynta ER label, August, 2011, JAN-MS-02544901

408. After \$1 billion in Nucynta IR and ER sales through 2014,⁸²⁴ Janssen sold the rights to Nucynta IR and ER to Depomed in 2015, for \$1.05 billion.⁸²⁵

409. As discussed below, the marketing messaging utilized by Janssen to promote Nucynta, like those developed by Purdue for OxyContin, overstated its benefits and understated its risks, but also sought to distinguish Nucynta from OxyContin/oxycodone in order to claim market share.

1. Janssen's Marketing Strategy for Nucynta

(a) Covering Acute to Chronic Continuum

410. Nucynta represented Johnson & Johnson's and Janssen's entry into the oral opioids market. It also represented the first "new molecule" centrally-acting opioid analgesic in 25 years, as Janssen's marketing materials asserted.⁸²⁶

411. From the outset, Janssen planned to introduce both IR and ER formulations of Nucynta, with their anticipated approvals about one year apart.⁸²⁷ They were both addressed in the same pre-launch business plans,⁸²⁸ in which Janssen discussed how the IR formulation would pave the way for the subsequent adoption of the ER formulation by prescribers, allow for coverage of the full spectrum of pain from acute to chronic in one molecule, and thereby give the drug a competitive advantage against OxyContin/oxycodone:

⁸²³ Nucynta ER Supplemental Approval Letter, August 28, 2012, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/200533Orig1s001ltr.pdf (last visited March 20, 2019)

⁸²⁴ PPLP003364349.

⁸²⁵ JAN-MS-00264775.

⁸²⁶ JAN-MS-00477361 at 4.

⁸²⁷ JAN-MS-00477361 at 4.

⁸²⁸ JAN-MS-00443233 ("Tapentadol Business Plan 2008," dated September 2007); JAN-MS-00477361 ("2009 Tapentadol Business Plan Situation Assessment," dated June 2008); JAN-MS-00350627 ("Nucynta (IR and ER) 2010 Business Plan," dated May 2009).

411.1. In its 2008 Business Plan for Tapentadol, Janssen set out a “Market Strategy” timeline to “accelerate adoption” in which it would “Generate successful experience with IR in 2009,” and then “Drive ER adoption leveraging clinical success with IR” in 2010.⁸²⁹

411.2. In its 2009 Tapentadol Business Plan, Janssen noted that “Back and Neck patients are the “sweet-spot” and the common path between IR to ER.”⁸³⁰

411.3. The same 2009 Business Plan described a “Tapentadol ER and IR US Market Strategy” to “Generate rapid adoption of IR rationalizing first choice use and pave the market introduction of the ER formulation.”⁸³¹

411.4. Janssen’s 2010 Nucynta IR and ER Business Plan contained a slide entitled “Message Strategy Evolution,” which showed its promotional messaging strategy dovetailing with the introduction of IR and then ER. It noted “Benefits of IR to ER transition vs Oxy.”⁸³²

411.5. Another “Message Evolution” slide in the 2010 Business Plan showed that in 2010 Janssen would “Build on SAO [short acting opioids] Experience” with Nucynta IR to “Replace OxyContin;” in 2011 it would “Expand to Broad Chronic Pain Types” to “Continue to Replace Oxy;” and in 2012 it would achieve a “Foundation of Management for both SAO and LAO to include the full spectrum of pain.”⁸³³

⁸²⁹ JAN-MS-00443233 at 13.

⁸³⁰ JAN-MS-00477361 at slide 12.

⁸³¹ *Id.* at slide 27.

⁸³² JAN-MS-00350627 at slide 34.

⁸³³ *Id.* at slide 38.

411.6. In the same Business Plan, Janssen identified “Evolve the value discussion to displace the oxycodone molecule” as a “Strategic Driver” of growth, and “Own the tapentadol patient from IR to ER (patient continuum)” (emphasis added) as the corresponding “Executional Driver.”⁸³⁴

411.7. In its 2011 Nucynta ER Launch Plan, Janssen noted that “Introduction of ER expands NUCYNTA molecule to compete in total moderate to severe pain market.” The slide showed that Janssen anticipated a total of 70 million prescriptions between IR and ER, and quoted a prescriber as stating, “The (acute/chronic) lines blur because of the ‘acute on chronic’ situation.”⁸³⁵

412. Janssen’s launch plans noted that acute pain can lead to chronic pain, and sought to leverage this through offering the two Nucynta formulations, IR and ER. In Janssen’s April 2009 “Market Overview Strategic Plan,” a slide entitled “Tapentadol – Pain Management Success Redefined” indicated that “Under-Management Driven by Side Effects” leads to “Severe Consequences,” causing a progression from “Acute pain to Chronic Pathology.” The slide also showed “Tapentadol IR—Redefines Pain Outcomes” leading to “Tapentadol ER—Optimizes Pain Outcomes.”⁸³⁶

413. At the same time, however, Janssen’s launch plans show it planned to market Nucynta IR as a way to *prevent* acute pain from becoming chronic pain. The Market Overview Strategic Plan included “Elevate the concept of early, effective acute pain management to limit

⁸³⁴ JAN-MS-00350627 at slide 40 (emphasis added).

⁸³⁵ JAN00012142 at 33.

⁸³⁶ JAN-MS-00457581 at 9.

pain progression” and “Potentially reduce the risk for the development of chronic pain” as objectives.⁸³⁷

(b) Disrupting the Complacent Market

414. Early on, Janssen identified “complacent” or “habitual” prescribing as a hurdle to Nucynta’s success, and its launch materials speak of the need to “disrupt” this status quo.

414.1. In its 2008 Tapentadol Business Plan, Janssen identified “Habitual market fraught with skepticism” as a “Lesson learned,” as to which the “Action to be taken” was “Establish receptivity to a NME [new molecule].” Another “Lesson learned” listed on the same slide was “Need to disrupt the marketplace in order to accelerate Tapentadol’s uptake,” with the “Action to be taken” “Integrate aggressive pre-marketing un-branded messages.”⁸³⁸

414.2. The same Business Plan noted that there was a “Habitual market dominated by generics” and that Janssen’s strategy for market entry should “balance the ability to break habitual prescribing vs. the risk of ‘niching’.”⁸³⁹

414.3. Similarly, Janssen’s 2009 Tapentadol Business Plan noted that there was a “Generic dominant, habitual and satisfied/complacent market” among prescribers.⁸⁴⁰ The first “Market Entry Approach” for Nucynta IR and ER listed in this Business Plan was “Successful unbranded campaign to disrupt the market place through flawless field launch readiness.”⁸⁴¹

⁸³⁷ *Id.* at 31.

⁸³⁸ JAN-MS-00443233 at 2.

⁸³⁹ *Id.* at 3.

⁸⁴⁰ JAN-MS-00477361 at 12.

⁸⁴¹ *Id.* at 27 (emphasis in original).

414.4. Janssen's 2009 "Market Overview Strategic Plan" likewise referenced a need for/to "Disrupting the Complacent Marketplace," "Disrupt the habitual generic marketplace" and "disrupt the market place in the unbranded followed by branded phases."⁸⁴² It also answered the strategy question of "What do we need to do?" with "Disrupt the satisfied marketplace."⁸⁴³

414.5. The same Strategic Plan identified "Habitual and Seemingly Satisfied Prescribing" as a "Key Challenge for Entering the CII Opioid Market," and "Satisfied, habitual prescribing by physicians" as a "Market Entry Hurdle" calling for disruption."⁸⁴⁴

414.6. A 2010 Nucynta Business Plan also identified "Habitual and Seemingly satisfied marketplace" as a challenge, and listed on a slide regarding "payer feedback" "**Largely satisfied market** (low level of perceived unmet need)."⁸⁴⁵

(c) Pre-Market FDA Statements Regarding the Safety and Efficacy of Nucynta IR

415. In the context of the growing abuse crisis, the FDA was concerned about the potential for abuse with Nucynta, as shown by pre-approval communications between Janssen and FDA. FDA also raised concerns about Janssen making unsubstantiated comparative and/or superiority claims comparing Nucynta and oxycodone.

416. In a November 20, 2008 FDA Memorandum re: Labeling Addendum incorporated into FDA's Medical Review(s) of the NDA for Nucynta IR of the same date, FDA stated that its Controlled Substances Staff, in their review of the abuse liability data, "noted that studies with tapentadol had findings consistent with a very high abuse liability (similar to

⁸⁴² JAN-MS-00457581 at 15, 35.

⁸⁴³ *Id.* at 102.

⁸⁴⁴ *Id.* at 6, 128, 152.

⁸⁴⁵ JAN-MS-00350627 at 7, 25 (emphasis in original).

hydromorphone),” and therefore found that “additional patient education is considered prudent and necessary to mitigate abuse.”⁸⁴⁶ FDA stated that a Medication Guide was thus being added to the drug’s labeling.

417. In the Risk Benefit Analysis summary of the Medical Office Review (“MOR”) of Nucynta IR, FDA’s Clinical Team Leader Dr. Ellen W. Fields found that Nucynta IR had “a safety profile very similar to that of other immediate release opioid analgesics and tramadol” and that “The risk/benefit analysis for tapentadol IR [wa]s similar to that of other opioid analgesics and Tramadol.”⁸⁴⁷

418. Dr. Fields further observed in the Risk Benefit Analysis that in a Phase 1 study, tapentadol was found to have an abuse liability similar to hydromorphone. She also noted that when subjects in a Phase 3 study abruptly discontinued tapentadol, 17% experienced at least one withdrawal symptom.⁸⁴⁸

419. In a discussion of this Phase 3 study later in the MOR, it is noted that the percentage of subjects with objective signs of withdrawal using the Clinical Opiate Withdrawal Scale (COWS) was 17% in the tapentadol group and 29% in the oxycodone group.⁸⁴⁹ It is also noted, however, that using the Subjective Opiate Withdrawal Scale (SOWS), there was no

⁸⁴⁶ Center for Drug Evaluation and Research, APPLICATION NUMBER:22-304, MEDICAL REVIEW(S), Part 1, at 3. available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_MedR_P1.pdf (last visited March 20, 2019), FDA Memorandum re: Labeling Addendum dated November 20, 2008, part of FDA’s Medical Review(s) of Tapentadol of the same date

⁸⁴⁷ Center for Drug Evaluation and Research, APPLICATION NUMBER:22-304, MEDICAL REVIEW(S), Part 1. at 9. available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_MedR_P1.pdf (last visited March 20, 2019), FDA Medical Officer Review for Tapentadol, January 23, 2008

⁸⁴⁸ *Id.*

⁸⁴⁹ Center for Drug Evaluation and Research, APPLICATION NUMBER:22-304, MEDICAL REVIEW(S), Part 2. at 71, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_MedR_P2.pdf (last visited March 20, 2019), FDA Medical Officer Review for Tapentadol, January 23, 2008, at 153.

statistically significant difference in the withdrawal severity between the two groups, and the same percentage in the two groups experienced drug withdrawal syndrome.⁸⁵⁰

420. The MOR included under “Recommendations for Postmarketing Risk Management Activities” a “Tapentadol IR Safety Surveillance Plan” Janssen had submitted on FDA’s request,⁸⁵¹ in which Janssen listed “potential for abuse” as an “important identified risk,” and “potential for...patient misuse” and “diversion” as “important potential risks.”⁸⁵²

421. Janssen also asked FDA whether it could make comparator/superiority claims for Nucynta in its labeling and marketing as early as 2003. FDA’s minutes from a November 13, 2003 “Type C Industry Meeting” with Janssen regarding development of the compound state:

The sponsor asked whether they may list the AEs of active comparators. Dr. Hertz said that this would not be allowed. Comparative claims carry a high burden of proof and must be replicated. Any mention of comparative data will be removed completely from the label unless there is an adequate body of evidence to justify its inclusion....The sponsor asked about the policy on comparative data as it relates to promotional material. Dr. Hertz said that that would need to be evaluated by the Division of Drug Marketing and Communication (DDMAC). Dr. Permutt clarified that a replicated head-to-head comparison of study drug with a comparator would be required to obtain a superiority claim.⁸⁵³

422. FDA reinforced this point over three years later when Janssen again raised making comparator or superiority claims at a pre-approval meeting with the FDA on June 5, 2007. The FDA’s meeting minutes indicate that Janssen sought to include on the Nucynta IR label a non-inferiority analysis comparing the potency of Nucynta to oxycodone. Dr. Hertz of

⁸⁵⁰ *Id.* at 72.

⁸⁵¹ JAN-0004-0013922 (“We also note the draft proposal does not include detailed information about surveillance and intervention components to monitor for appropriate use and abuse, which are important elements of many of the current risk management programs for opioids. Please remember to submit all planned materials identified within the RiskMAP that will be necessary to implement your proposal.”) *Id.* at 16.

⁸⁵² Center for Drug Evaluation and Research, APPLICATION NUMBER:22-304, MEDICAL REVIEW(S), Part 1. at 9-10. available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_MedR_P1.pdf (last visited March 20, 2019), FDA Medical Officer Review for Tapentadol, January 23, 2008.

⁸⁵³ JAN-MS-01031602 at 6.

FDA “responded that this type of information would not be considered appropriate for inclusion in the label.”⁸⁵⁴

(d) Pre-Market FDA Statements Regarding the Safety and Efficacy of Nucynta ER

423. FDA also raised concerns regarding the potential for abuse and dependence of Nucynta ER prior to its approval. In a September 9, 2010 Memorandum to Dr. Bob Rappaport, FDA’s Director of the Division of Anesthesia and Analgesia Products (“DAAP”), from Dr. Alicja Lerner, a Medical Officer with FDA’s Controlled Substance Staff, concerning Nucynta ER, Dr. Lerner stated, “This is our response to the DAAP consult regarding the abuse related safety issues, including overdose, withdrawal, misuse and abuse of Nucynta ER (Tapentadol ER).”⁸⁵⁵ Dr. Lerner concluded that:

423.1. “The controlled release properties of the TRF [tamper resistant formulation] formulation can be readily overcome by multiple simple physiochemical manipulations.”^{856 857}

423.2. “The to be marketed formulation [also referred to as TRF] exhibits an increased frequency of abuse related adverse events.”⁸⁵⁸

423.3. “In a Phase 1 study in healthy subjects (R331333-PAI-1028), 50% of the [TRF] subjects exhibited euphoria at 250mg.”⁸⁵⁹

⁸⁵⁴ JAN-0004-0013922 at 9.

⁸⁵⁵ Center for Drug Evaluation and Research, APPLICATION NUMBER: 200533Orig1s000, OTHER REVIEW(S), at 70-74, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200533Orig1s000OtherR.pdf (last visited March 20, 2019), Letter from Dr. Nelson to Dr. Rappaport dated September 9, 2010.

⁸⁵⁶ *Id.* at 71.

⁸⁵⁷ What was referred to as the “TRF” formulation in the NDA was what was approved and marketed as Nucynta ER.

⁸⁵⁸ *Id.* at 72.

423.4. “In the pooled AE analysis Phase 1 single-dose studies, 5.5% of [TRF] subjects exhibited euphoria, and 8.1% of subjects reported ‘feeling drunk’ as compared to 1% and 0% subjects taking other ER formulations, respectively.”⁸⁶⁰

423.5. “Further, withdrawal symptoms, including insomnia, depressed mood, depression, suicidal ideation, and disturbance in attention, occurred after Tapentadol ER was stopped. Such withdrawal symptoms are common to all mu agonist opioids.”⁸⁶¹

424. Dr. Lerner’s recommendations based on these conclusions included:

424.1. “Because the drug product at the 250 mg dose level appears to result in a high percentage of euphoria and other Opioid like adverse events, the sponsor must provide an adequate rationale for marketing the dose, so that the benefits continue to outweigh the risks.”⁸⁶²

424.2. “Upon approval and marketing, the drug product should continue to be monitored for abuse, misuse, overdose, and withdrawal.”⁸⁶³

425. A July 12, 2011 Memorandum from Dr. Lerner to Dr. Rappaport concerning Nucynta ER reiterated the conclusions in the September 2010 memo, and also noted that “the TRF formulation, in particular the dose of >150mg, appears to exhibit an increased frequency of adverse events (e.g. euphoria) signaling abuse potential.”⁸⁶⁴

⁸⁵⁹ *Id.* at 72.

⁸⁶⁰ *Id.* at 72.

⁸⁶¹ *Id.* at 72.

⁸⁶² *Id.* at 72.

⁸⁶³ *Id.* at 73.

⁸⁶⁴ Center for Drug Evaluation and Research, APPLICATION NUMBER: 200533Orig1s000, OTHER REVIEW(S), at 38-42, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200533Orig1s000OtherR.pdf (last visited March 20, 2019), July 12, 2011 letter from Dr. Lerner to Dr. Rappaport.

426. Dr. Lerner's conclusions and recommendations were included in the Medical Review(s) for Nucynta ER dated July 29, 2011.⁸⁶⁵ However, in a subsequent August 3, 2011 letter from the Director of FDA's Controlled Substances Staff, Dr. Michael Klein, to Dr. Rappaport, Dr. Klein withdrew Dr. Lerner's recommendations and conclusions from the September 9, 2010 memo following a meeting with the Controlled Substances Staff and Office of Clinical Pharmacology (OCP).⁸⁶⁶ Dr. Klein found that Dr. Lerner's adverse event analysis "covered a limited area of investigation," and that her conclusions "are insufficient to override the analyses and conclusions of the reviewer of the full range of clinical studies."

427. Left unchanged by the August 3, 2011 memo was the Summary Review for Regulatory Action included in the Medical Review(s), dated October 1, 2010, which stated that, "With respect to specific safety concerns, such as abuse potential, dependence, withdrawal and neuropsychiatric adverse events, the safety profile of extended-release tapentadol appeared to be consistent with other products with similar pharmacologic properties. There is suggestion that extended-release tapentadol may have abuse potential and dependence/withdrawal characteristics similar to long acting opioids."⁸⁶⁷

428. Janssen sought FDA's authorization to include a Tamper Resistant Formula (TRF) claim on the Nucynta ER label, but FDA did not permit the labeling claim. Upon review of the

⁸⁶⁵ Center for Drug Evaluation and Research, APPLICATION NUMBER: 200533Orig1s000, MEDICAL REVIEW(S), at 8-9, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200533Orig1s000MedR.pdf (last visited March 20, 2019), FDA Medical Review(s) for Nucynta ER, July 29, 2011.

⁸⁶⁶ Center for Drug Evaluation and Research, APPLICATION NUMBER: 200533Orig1s000, OTHER REVIEW(S), at 12-14, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200533Orig1s000OtherR.pdf (last visited March 20, 2019), August 3, 2011 letter from Dr. Klein to Dr. Rappaport.

⁸⁶⁷ Center for Drug Evaluation and Research, APPLICATION NUMBER: 200533Orig1s000, MEDICAL REVIEW(S), at 67, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/200533Orig1s000MedR.pdf (last visited March 20, 2019), FDA Summary Review for Regulatory Action, October 1, 2010, at page 12.

TRF data Janssen provided, FDA found that the data “shows that none of these studies are robust and compelling enough to support abuse-deterrent Tier 1, 2, or 3 labeling claims for various routes of administration.”⁸⁶⁸

429. When Janssen invoked the “low rate of abuse” in the postmarketing data for Nucynta IR and ER in support of its request for TRF labeling, FDA responded:

The low rate of abuse of both tapentadol IR and ER in the community is promising, *but the data do not yet provide sufficient evidence to confer a Tier 4 claim for Nucynta ER. At this point in time, it is unclear whether the relatively low amount of abuse detected is due to a low level of awareness of the drug as a consequence of its short marketing history, low utilization, reduced opioid receptor affinity of the tapentadol molecule, or the tamper resistant characteristics of the extended-release formulation.* Due to the lack of a non-abuse-deterrent comparator, detecting meaningful change in the level of community abuse is challenging. You have chosen adequate data sources to depict the current extent of abuse in the community, but *the limited time frame each data source portrays is insufficient to characterize the abuse profile of Nucynta ER.* To determine if the current trend remains stable over time, continued surveillance and monitoring of Nucynta ER is necessary. The amount of data needed to determine if a trend is stable varies by situation, and the low utilization level for Nucynta ER may extend that time period. Additionally, *the data must be able to show that the smaller amount of abuse in the community is contingent on the drug formulation, and not due to its low utilization or to innate properties of the molecule itself.*⁸⁶⁹

430. I have not located in the record a submission by Janssen of additional data of the type FDA requested, and the Nucynta ER label was never changed to include a TRF claim.

2. Janssen’s Marketing of Nucynta Overstated its Benefits.

431. Janssen’s marketing adopted “powerful efficacy with unprecedented tolerability” as the key promotional tagline for “disrupting” the “complacent” or “satisfied” opioid market.⁸⁷⁰ Three primary messages of this approach were 1) a unique dual mechanism of action that would

⁸⁶⁸ FDA Preliminary Meeting Comments, August 5, 2013, JAN-MS-02043301 at 3.

⁸⁶⁹ JAN-MS-02043301 at 6-7 (emphasis added) , FDA Preliminary Meeting Comments, August 5, 2013.

⁸⁷⁰ JAN-MS-00477361 at 24; JAN-MS-00457581 at 89; JAN00012142 at 8.

increase efficacy; 2) fewer gastrointestinal (“GI”) side effects; and 3) less abuse liability and withdrawal.

432. These were the first three “Key attributes perceived to differentiate [Nucynta] from existing chronic pain medications” identified in an August 2010 Nucynta ER Payer and Physician Research PowerPoint: “Increased tolerability due to lower GI side effects;” “Decreased abuse potential and tamper-resistant properties;” “Dual mechanism of action.”⁸⁷¹

433. These messages were used to differentiate Nucynta from other analgesics, particularly OxyContin/oxycodone. In my opinion, these superiority claims were neither contained in the label nor supported by substantial evidence, and overstated Nucynta’s benefits while understating its risks.

(a) Janssen Overstated the Benefits of Nucynta’s Mechanism of Action

434. The Nucynta IR and ER labels have stated from the beginning that tapentadol’s exact mechanism is unknown. Through 2010, the IR label additionally stated that “its effect is thought to be due to mu-opioid agonist activity and the inhibition of norepinephrine reuptake.”⁸⁷² As of 2013, this language changed to “Although the clinical relevance is unclear, preclinical studies have shown that tapentadol is a mu-opioid receptor (MOR) agonist and a norepinephrine reuptake inhibitor (NRI). Analgesia in animal models is derived from both of these properties.”⁸⁷³ The latter language has been the language used in the Nucynta ER label since approval.

⁸⁷¹ JAN-MS-00473858 at 36

⁸⁷² Nucynta IR label, 2008, JAN-MS-00445032; Nucynta IR label, 2009, JAN-MS-01249732; Nucynta IR label, 2010, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022304s0031bl.pdf (last visited March 20, 2019)

⁸⁷³ Nucynta IR label, July 2013, JAN-MS-01229368; Nucynta IR label, October 2013, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022304s014s0151bl.pdf (last visited March 20, 2019); Nucynta IR label, December 2016, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022304s0161bl.pdf (last visited March 20, 2019);

435. Prior to launching Nucynta, Janssen identified its purported “unique dual mechanism of action” as a primary means to differentiate the drug from competitors and “disrupt” habitual prescribing. Janssen’s launch materials indicated it planned to use this message to suggest that Nucynta had unique efficacy in “mixed” pain, and that it reduced the need for patients to take additional opioids (a characteristic referred to by Janssen as “opioid sparing”).

435.1. Janssen’s 2008 Tapentadol Business Plan noted that a “Key IR Message” and “Value Proposition” for Nucynta IR was that it was a “Centrally acting analgesic with dual mechanism of action.”⁸⁷⁴

435.2. The same 2008 Business Plan stated on a slide entitled “Phase IV Clinical Development Strategies” “Bridge the gap between pre-clinical and clinical perspective regarding MOA--Demonstrate versatility of the molecule in PCP- relevant pain models.” The slide suggested that the “Dual MoA” led to greater efficacy and safety.⁸⁷⁵

435.3. The 2008 Business Plan further stated on a “Brand Vision” slide that the dual MOA had “‘Opioid Sparing’ Effects” which would mean less withdrawal symptoms and less dose escalation.⁸⁷⁶ No evidence was cited for these claims.

Nucynta IR label, September 2018, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022304s019s0211bl.pdf (last visited March 20,2019); Nucynta ER label, 2011, JAN-MS-02544901; Nucynta ER label, July 2012, JAN-MS-00229587; Nucynta ER label, August 2012, JAN-MS-00229558; Nucynta ER label, April 2014, JAN-MS-03088328; Nucynta ER label, December 2016, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/200533s0141bl.pdf (last visited March 20,2019); Nucynta ER label, September 2018, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/200533s018s0191bl.pdf (last visited March 20,2019).

⁸⁷⁴ JAN-MS-00443233 at 10.

⁸⁷⁵ *Id.* at 11.

⁸⁷⁶ *Id.* at 12.

435.4. A September 2008 press release Janssen drafted in anticipation of Nucynta IR's approval stated "Nucynta has a unique profile with two mechanisms of action, combining mu-opioid receptor agonism and norepinephrine reuptake inhibition in a single molecule."⁸⁷⁷ In a September, 2008 email chain addressing the draft, Janssen executive Kathleen Dusek stated that based on a review of an FDA warning letter, the word "unique" (among others in the press release) "might be contentious," and went on to assert "We do not have clinical data to support the dual mechanism of action. Generally, FDA feels that preclinical evidence is not enough."⁸⁷⁸ The language Dusek identified was removed from the final version of the press release, but the company continued to tout the the benefits of Nucynta's dual MoA in its promotional materials, as noted below.

435.5. In a SWOT analysis in its 2009 Tapentadol Business Plan, Janssen listed among Nucynta's strengths "Dual Mechanism of Actions in 1 molecule," but then listed among its weaknesses "Norepinephrine benefit not clear/quantifiable."⁸⁷⁹

435.6. In its 2009 "Marketing Overview Strategic Plan," Janssen again stated that the drug's "Dual MOA-Opioid Sparing Effects" was a "Value Proposition" that would lead to "less withdrawal symptoms," "less dose escalation (durability)," and "emotional wellbeing."⁸⁸⁰ No evidence was cited for these claims.

⁸⁷⁷ JAN-MS-01124875 at 2-4.

⁸⁷⁸ JAN-MS-01124875.

⁸⁷⁹ JAN-MS-00477361 at 19, 20.

⁸⁸⁰ JAN-MS-00457581 at slide 10.

435.7. Another slide in the 2009 Plan stated “The μ -opioid-sparing effect message should be emphasized (opiophobia is common in primary care).”⁸⁸¹

435.8. In a slide in the same 2009 Plan on “Optimizing Analgesic Therapy for Moderate to Severe Pain,” Janssen listed an objective of “Highlight recent research supporting the benefits of multi-modal therapy to maximize analgesic efficacy and minimize side effects” in order to “Set the stage for introduction of tapentadol,” “An agent with mu-opioid agonist and NE-reuptake inhibition mechanisms of analgesia.”⁸⁸² No such research was cited.

435.9. In slides in the same 2009 Plan regarding speaker and KOL engagements, unbranded publications, and secondary publications, Janssen’s notes to the slides stated these would “Support the rationale for an agent with two MOAs.”⁸⁸³

435.10. A “Tested Positioning Statement” in the 2009 Plan presented a “The Best of Both Worlds” statement. This statement asserted that Nucynta provided “pain relief without tradeoffs,” which was unsupported by substantial evidence:

Product X [Nucynta] is the only *dual-acting*, single-agent, Schedule II analgesic linking powerful opioid efficacy with unprecedented tolerability that enables physicians to provide *pain relief without tradeoffs* because it *selectively works on both the mu-opioid and norepinephrine pathways for optimal pain control* without treatment-compromising side effects.⁸⁸⁴

435.11. An “APS [American Pain Society] Activities” section of the 2009 Plan indicated that Janssen would be sponsoring an APS booth that would feature several

⁸⁸¹ *Id.* at 41.

⁸⁸² *Id.* at 33.

⁸⁸³ *Id.* at 35, 49, 153.

⁸⁸⁴ *Id.* at 89 (emphasis added).

Janssen posters, including one called “Pathways,” which stated “Multimodal pathways that address more than one pathway may provide more comprehensive relief.”⁸⁸⁵

435.12. Janssen’s 2010 Nucynta Business Plan identified as a “lever of growth” “Drive the **mixed / multi-etiology of pain consideration for a broader pain types using the dual MOA followed by DPN findings as the proof of concept and** rational [sic] for first line / foundation of management.”⁸⁸⁶

435.13. Two slides later, however, the 2010 Business Plan recognized as a “challenge” the fact that “MOA is a proof of concept only.”⁸⁸⁷

435.14. Similarly, a slide in the 2010 Plan listing “Strengths” notes “Dual MOA resonates with mu-receptor sparing effects,” but the next slide on “Weaknesses” noted “Norepinephrine benefit not clear/quantifiable.”⁸⁸⁸

435.15. Janssen’s 2011 Nucynta ER Launch Plan identified “Unique Mechanism of Action” as a “Nucynta ER Core Message,” and asserted that “Unlike traditional opioids, Nucynta has 2 proven analgesic mechanisms.”⁸⁸⁹

435.16. The 2011 ER Launch Plan also indicated that in a presentation on osteoarthritis data for Nucynta, physicians identified the key message as “A new pain medication with equal or greater efficacy than OxyContin, but fewer side effects, less discontinuation and a dual MOA.”⁸⁹⁰

⁸⁸⁵ *Id.* at 54, 65.

⁸⁸⁶ JAN-MS-00350627 at 5. (Emphasis in original.)

⁸⁸⁷ JAN-MS-00350627 at 7.

⁸⁸⁸ JAN-MS-00350627 at 10, 11.

⁸⁸⁹ JAN00012142 at 8.

⁸⁹⁰ *Id.* at 22.

435.17. A slide entitled “Tapentadol answers the unmet need” in the 2011 Launch Plan contained the position statement that Nucynta is “the only broad coverage analgesic that provides superior outcomes” because... “Dual MOA, (MU/NRI) provide opioid-sparing benefits.”⁸⁹¹

436. Once Nucynta was on the market, Janssen continued to promote the purported “unique dual mechanism of action” of Nucynta as a primary means to differentiate the drug from competitors and “disrupt” habitual prescribing. Janssen’s marketing materials falsely suggested that this mechanism imparted to Nucynta unique efficacy in certain types of pain, particularly back and neck pain, and reduced the need for patients to take additional opioids.

436.1. A May 2010 recap of a “Nucynta Ask the Expert Call” for sales representatives shows that in response to a discussion of the norepinephrine mechanism, Janssen suggested that the representatives “d[idn’t] need to get into the science” but should ask, “Why would you not use a drug that hits pain from multiple pathways?”⁸⁹² In the Nucynta FAQ (Frequently Asked Questions) referred to in the recap, the response to the FAQ of “What is the contribution of analgesia of NUCYNTA through mu-receptor agonism and norepinephrine reuptake inhibition?” is “This is currently being investigated by Grunenthal and at this point we cannot comment.”⁸⁹³

436.2. In Janssen’s 2012 Nucynta and Nucynta ER Business Plan, Janssen laid out a marketing strategy to “generate data to support MoA differentiation” in order to “strengthen differentiation and value through new & compelling evidence.”⁸⁹⁴

⁸⁹¹ *Id.* at 30.

⁸⁹² JAN-MS-03007471; JAN-MS-03007472

⁸⁹³ JAN-MS-03024758; JAN-MS-03024760.

⁸⁹⁴ JAN-MS-00010801 at 12, 42.

436.3. A SWOT analysis in the 2012 Business Plan identified among the drug's strengths "New molecular entity (dual MOA)," and among its opportunities "MOA & GI Tolerability benefits more meaningful in chronic pain."⁸⁹⁵

436.4. A "Pain Business Review" for Nucynta IR & ER dated April 23, 2014 contained a "NUCYNTA ER Positioning Statement" asserting that Nucynta "offers a superior overall clinical profile **because**: it provides best-in-class efficacy across multiple pain types... and a unique dual MOA **so that**: physicians and patients can achieve their individualized pain improvement goals without many of the challenges typically associated with traditional opioids."⁸⁹⁶ No evidence was cited to support these claims.

436.5. The Review identified among the "RTBs [reasons to believe]" for the Positioning Statement the following: "Dual MOA with mu-opioid agonism and norepinephrine reuptake inhibition."⁸⁹⁷

437. In his deposition, Janssen's former Director of Sales and Marketing, David Lin, testified that the dual mechanism was based solely upon pre-clinical animal studies.⁸⁹⁸ He also agreed that "if the exact mechanism of action is unknown, that renders it difficult, if not impossible, to unequivocally make statements about dual mechanism of action."⁸⁹⁹

438. Janssen's sales call notes show that its sales representatives nonetheless frequently promoted Nucynta's "unique" "dual" mechanism of action to healthcare providers,

⁸⁹⁵ *Id.* at 61.

⁸⁹⁶ JAN-MS-02389698 at 73 (emphasis in original).

⁸⁹⁷ *Id.* at 74.

⁸⁹⁸ David Lin Dep., 91:12 -95:4 (December 20, 2018).

⁸⁹⁹ David Lin Dep., 74:5 -79:12 (December 20, 2018).

without the qualification on the label that the exact mechanism is unknown. The large majority of call notes for Nucynta make these unsupported claims. For example:

438.1. One Illinois call note from July 2009 reports, “I was able to speak with dr Chami about the advantages of having the dual MOA and he told me that he can see how Nucynta would benefit his patients. He also felt that this could keep him from having to use two pain meds for treatment of the back and neck pain patient.”⁹⁰⁰

438.2. Another Illinois call note from that same month described speaking “with the dr about the fact that Nucynta Dual MOA and what advantages Nucynta will provide patients that suffer from Back and neck pain.”⁹⁰¹

438.3. A Wisconsin call note from August 2009 states that the sales representative “discussed Nucynta's dual moa and how it could help provide more of a comprehensive approach to pain management, along with comparable efficacy to oxy ir as well as an excellent safety profile makes Nucynta an ideal treatment option to pts with acute pain askd her what her hesitation was in trialing Nucynta, she indicated its newness.”⁹⁰²

438.4. From 2013 to 2015, “MOA” or “Mechanism of action – Nucynta ER” was listed as the message for 89 sales calls or visits for Nucynta ER.⁹⁰³

439. In my opinion, Janssen overstated the benefits of Nucynta’s mechanism of action, promoting it as offering increased efficacy and fewer side effects without substantial evidence.

⁹⁰⁰ JAN00118971. Additional call notes can be found in Schedule 11.

⁹⁰¹ *Id.*

⁹⁰² *Id.*

⁹⁰³ JAN00118960.

(b) Janssen Overstated the Benefits of Nucynta's GI Tolerability

440. Prior to launching Nucynta, Janssen identified the drug's purportedly superior GI tolerability as another principal means of differentiating the drug from competitors and "disrupting" "satisfied" prescribing. Janssen's launch materials indicated it planned to highlight this message from the outset.

440.1. In one of its earliest launch plans for Nucynta, Janssen identified "Improved GI Tolerability (Nausea & Vomiting)" as a "Key product attribute."⁹⁰⁴

440.2. In its 2008 Tapentadol Business Plan, Janssen identified "Integrate aggressive pre-marketing un-branded messages--Unmet need (GI, CNS)" as an "Action to be taken" "to disrupt the marketplace" and "accelerate Tapentadol's uptake."⁹⁰⁵

440.3. In the 2008 Plan Janssen also identified "Amplify tolerability (GI; CNS) with additional safety markers" as an "execution driver" for the "brand strategy" of "Establishing a differentiated and customer-compelling value proposition to get most favorable formulary access."⁹⁰⁶

440.4. The 2008 Business Plan also noted that a "Key IR Message" and "Value Proposition" for Nucynta IR was "*GI Tolerability superior to oxycodone* at comparable doses (NI Study)"⁹⁰⁷ (emphasis added).

440.5. Janssen's 2009 Business Plan for Nucynta asserted that Nucynta had "Typical opioid-related AEs, but, compared with oxycodone at equipotent doses: Less constipation; Less nausea – **superiority claim at launch**; Less vomiting - **superiority**

⁹⁰⁴ JAN-MS-01053692 at slide 15.

⁹⁰⁵ JAN-MS-00443233 at slide 2.

⁹⁰⁶ *Id.* at 4.

⁹⁰⁷ *Id.* at 10 (emphasis added).

claim at launch” (bold emphasis added).⁹⁰⁸ The support cited for these claims consisted of tolerability studies lasting 3 to 90 days.

440.6. The 2009 Business Plan identified as a “Market Entry Approach” for Nucynta IR and ER “Timely completion of differentiation studies including the bunionectomy additional end-stage OA to support superiority claims in GI side effects.”⁹⁰⁹

440.7. In a “Tapentadol Value Propositions” slide in Janssen’s 2009 “Marketing Overview Strategic Plan,” the drug’s “Lower side effect (GI and pruritis)” was cited in support of the value proposition of “Comprehensive Efficacy with Superior tolerability.”⁹¹⁰ No evidence was provided for the lower side effect claims, which did not appear on the drug’s label.

440.8. A slide from the 2009 Plan entitled “Current Treatment Dynamics” showed “Opioid induced GI side effects” leading to “Inadequate management of acute pain,” for which tapentadol would be a solution.⁹¹¹

440.9. An “APS [American Pain Society] Activities” section of the 2009 Plan indicated that Janssen would be sponsoring an APS booth that would feature several Janssen posters, including one regarding side effects, which characterized patients’ “concerns about opioid related GI side effects” as a “barrier that leads to undertreatment of moderate to severe pain.”⁹¹²

⁹⁰⁸ JAN-MS-00477361 at 5 (emphasis added).

⁹⁰⁹ *Id.* at 27 (emphasis in original).

⁹¹⁰ JAN-MS-00457581 at 10.

⁹¹¹ *Id.* at 12.

⁹¹² *Id.* at 54, 65.

440.10. In the same Strategic Plan, Janssen instructed “Highlight the importance of side effects (especially constipation) as a culprit for achieving optimal management” as a “Seed of disruption” to address the “Market Entry Hurdle” of “Lack of patient-physician dialogue to surface patient dissatisfaction.”⁹¹³

440.11. The Strategic Plan also highlighted the value of marketing “Reduction of GI AEs” to pharmacists, recommending messages of “Reduced need for laxatives and other concomitant meds,” and “Shorter duration of GI AEs may improve compliance and overall QOL.”⁹¹⁴

440.12. “Offers GI tolerability that is superior to oxycodone in both opioid-naïve and opioid-experienced patients” and “Provides superior tolerability with a 50% reduction in GI-induced side effects vs. Oxycodone IR” are identified as “Brand Lifting” statements that are among the “Key Features to Keep in Messaging” in two different slides in the Strategic Plan.⁹¹⁵

440.13. A September 2008 press release Janssen drafted in anticipation of Nucynta IR’s approval stated, “The studies also showed that treatment with [Nucynta] for acute moderate to severe pain is associated with a favorable gastrointestinal side effect profile, compared to oxycodone, a commonly used prescription medication for moderate to severe pain.”⁹¹⁶ In a September 2008 email chain addressing the draft, Janssen executive Kathleen Dusek stated that “While we might be able to say ‘potential for a favorable GI side effect profile,’ ...the data in the NOA do not really support saying we

⁹¹³ *Id.* at 6, 128, 152 (emphasis in original).

⁹¹⁴ *Id.* at 45.

⁹¹⁵ *Id.* at 90, 92.

⁹¹⁶ JAN-MS-01124875 at 2-3.

have a favorable GI profile *against oxy.*”⁹¹⁷ The language Dusek identified was removed from the final version of the press release, but the company continued to tout Nucynta’s “better” GI tolerability in its promotional materials, as noted below.

440.14. A 2010 Nucynta Business Plan noted that while there was a “**Largely satisfied market** (low level of perceived unmet need),” “Physicians and patients identify AEs (particularly GI) as key areas of unmet need.”⁹¹⁸

440.15. Janssen’s 2011 Nucynta ER Launch Plan identifies “Better GI Tolerability” as a “Nucynta ER Core Message,” and beside it notes that “Fewer discontinuations means more patients can achieve pain relief.”⁹¹⁹

441. After launch, Janssen continued to promote the purported greater gastrointestinal tolerability of Nucynta as a key tool in differentiating the drug from competitors and “disrupting” “complacent” prescribing. Janssen’s marketing materials falsely suggested that Nucynta had demonstrated superiority over competitor drugs with regards to GI tolerability.

441.1. A SWOT analysis in Janssen’s 2012 Nucynta and Nucynta ER Business Plan identified among the drug’s strengths “Robust clinical data - proven efficacy vs std of care, better GI tolerability, (IR, ER),” and among its opportunities “MOA & GI Tolerability benefits more meaningful in chronic pain.”⁹²⁰

441.2. A “Video Walk –Through” sales aid and script dated June 6, 2012, contained a screen shot with a header stating “Make NUCYNTA ER Your Choice for Chronic Pain” along with tabs including “Dual Mechanism of Action,” “Efficacy,” and

⁹¹⁷ JAN-MS-01124875 (emphasis in original).

⁹¹⁸ JAN-MS-00350627 at 7, 25 (emphasis in original).

⁹¹⁹ JAN00012142 at 8.

⁹²⁰ JAN-MS-00010801 at 61.

“Tolerability/Safety/Withdrawal.” Notes underneath the screen shot state, “The low back pain study efficacy, the GI tolerability, and the withdrawal information continue to be the crux of the NUCYTNA ER story, and you should keep reinforcing these critical messages.”⁹²¹

441.3. A “Pain Business Review” for Nucynta IR & ER dated April 23, 2014 contained a “NUCYNTA ER Positioning Statement” asserting that Nucynta “offers a superior overall clinical profile **because**: it provides best-in-class efficacy across multiple pain types... [and] proven GI tolerability **so that**: physicians and patients can achieve their individualized pain improvement goals without many of the challenges typically associated with traditional opioids.”⁹²² No evidence was cited to support these claims.

441.4. The Review identified among the “RTBs [reasons to believe]” for the Positioning Statement the following: “Proven GI tolerability.”⁹²³

441.5. Several Janssen advertisements for Nucynta promoted its “unexpected tolerability” or “tolerability you want” with graphs showing GI tolerability data from clinical studies.⁹²⁴

442. On August 26, 2011, FDA’s DDMAC wrote to Janssen regarding oral statements made by a Janssen representative about Nucynta at a meeting of the American Society of Health-System Pharmacists, which FDA found to constitute unsubstantiated superiority claims and minimization of risk.⁹²⁵

⁹²¹ JAN-MS-00774016 at 6.

⁹²² JAN-MS-02389698 at 73 (emphasis in original).

⁹²³ *Id.* at 74.

⁹²⁴ JAN-MS-00236322 at 2; JAN-MS-00229217 at 5.

⁹²⁵ JAN-MS-02273742.

442.1. DDMAC reported that its representative observed the Janssen representative state at the meeting that “DPNP patients stay on Nucynta for longer, and Nucynta provides 10 mg of opioid/oxycodone pain control, similar to tramadol, but with less GI, constipation, nausea and vomiting.”⁹²⁶

442.2. DDMAC found that this statement “misleadingly implie[d] that Nucynta is clinically superior (i.e., safer) compared to oxycodone and tramadol for DPNP patients. Specifically, it implies that Nucynta has been shown to have less GI adverse reactions (i.e., constipation, nausea, and vomiting)...when this is not the case.”

442.3. FDA noted in the letter that when it reviewed the data from clinical studies for Nucynta involving subjects taking Nucynta and oxycodone, it “determined that the studies were not adequately powered for the analysis of multiple safety endpoints, and that the dose of oxycodone used as a comparator was not demonstrated to be equianalgesic to the doses of Nucynta studies. Therefore, safety comparative data were not considered clinically meaningful and were not included in the approved PII for Nucynta.”⁹²⁷

442.4. FDA further stated that “the sales representative’s claim that Nucynta results in less constipation, nausea and vomiting minimizes the risks associated with the use of Nucynta and suggests that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.”⁹²⁸

442.5. FDA noted that the most common adverse events associated with Nucynta in clinical studies included nausea and vomiting, “and these were also among the most

⁹²⁶ *Id.* at 2.

⁹²⁷ *Id.* at 4.

⁹²⁸ *Id.* at 4.

common reasons for discontinuation of treatment...Additionally, 8 percent of Nucynta-treated patients experienced constipation as an adverse event in clinical studies versus 3 percent in the placebo arm.”⁹²⁹

442.6. FDA requested that Janssen immediately cease its violative promotional activities for Nucynta, and list all “promotional materials for Nucynta that contain violations such as those above.”⁹³⁰

443. Janssen responded that it was “not aware of promotional activities or materials for Nucynta that contain statements/claims such as those described” in FDA’s letter.⁹³¹

444. The materials cited above, however, show that Janssen was in fact engaging in promotional activities containing statements like those described in FDA’s letter, and continued doing so even after its response.

445. In addition, Janssen’s sales call notes show that its sales representatives frequently promoted Nucynta as having lower rates of GI side effects. For example:

445.1. An Ohio call note from June 2009 reported, “The improved GI side effect profile of Nucynta does offer some advantages over some of the other branded IR opioid medications. Unlikely it would be a 2nd tier position, but would be tier 3 for most of Paramount’s plans. Customer was also curious of any evidence of less abuse potential compared to Oxycontin as an example. Significance: Nucynta with its additional GI

⁹²⁹ *Id.* at 4.

⁹³⁰ *Id.* at 4.

⁹³¹ September 12, 2011 letter from Roxanne O. McGregor-Beck, Janssen Associate Director of Regulatory Advertising and Promotion, to Dr. Mathilda K. Fienkeng, Regulatory Review Officer at FDA’s DDMAC. JAN-MS-00230368.

benefits would not likely to be disadvantaged for most plans, and would likely be a tier 3 opioid without restrictions.”⁹³²

445.2. A Wisconsin call note from September 14, 2009 reported, “Talked with Dr Kumar - he said he hasn't used it yet -- he just needs to get comfortable and he has all the information. I told him the only way he is going to get comfortable is to use. Referenced that ... patients are having improvements with tolerability. Pointed out the fact that patients have placebo-like constipation and over 50% less nausea and vomiting. I asked him to identify some patients who are having surgery done and write Nucynta instead of percocet for them so he can be more familiar with it...”⁹³³

445.3. From 2013-2015, there were 8 sales calls/visits for Nucynta ER that had “Proven Tolerability” reported as the key message.⁹³⁴

446. In my opinion, Janssen overstated the benefits of Nucynta’s GI tolerability, making superiority claims without substantial supporting evidence.

3. Janssen’s Promotion of Nucynta Minimized the Risks of Abuse and Withdrawal During an Opioid Abuse Epidemic.

447. Nucynta represented Johnson & Johnson’s and Janssen’s entry into the oral opioids market. At the time Nucynta was first approved at the end of 2008, that market had reached approximately \$7.5 billion in annual sales, with approximately \$2.5 billion in immediate release oral opioids and approximately \$4.6 billion in extended or continuous release oral

⁹³² JAN-OH-00000262. Additional call notes can be found in Schedule 11.

⁹³³ JAN00118971.

⁹³⁴ JAN00118960.

opioids.⁹³⁵ The extended release market was dominated by Purdue's OxyContin, which had \$2.2 billion in sales in 2008.⁹³⁶

448. By the time of Nucynta's approval, there was a growing public health crisis of opioid abuse, particularly of OxyContin/oxycodone, as documented and discussed by many news reports from wide-ranging geographic areas,⁹³⁷ by FDA in Advisory Committee meetings,⁹³⁸ by legal filings,⁹³⁹ and by medical journal articles⁹⁴⁰. As shown below, from early on, Janssen's promotional materials for Nucynta discussed the marketing impact of growing concerns about abuse and turning such concerns to Janssen's advantage. Janssen recognized internally that "increased use is associated with increased abuse and diversion,"⁹⁴¹ but sought to maximize sales of Nucynta while understating the risk of abuse and withdrawal and offering as "solutions" to the abuse problem tools such as its prescriberresponsibly.com website,⁹⁴² which minimized the risk of addiction through the concept of "pseudoaddiction."

449. Beginning prior to the approval of Nucynta, Janssen developed marketing plans identifying the medical community's concerns about abuse as a factor in marketing the drug. Those plans sought to allay those concerns, often through understating Nucynta's risk of abuse and withdrawal. At the same time, the plans sought to differentiate Nucynta from

⁹³⁵ Opioid sales totals for 2008 calculated from IQVIA (formerly IMS) data reported in PPLP003364349.

⁹³⁶ *Id.*

⁹³⁷ See PPLPC028000099480; See also PDD8107130029; See also Borger, Juliana. "Hillbilly Heroin: the Painkiller Abuse Wrecking Lives in West Virginia." The Guardian, 6 June 2001, available at <https://www.theguardian.com/world/2001/jun/25/usa.julianborger> (last visited March 20, 2019)..

⁹³⁸ See JAN-MS-00616428.

⁹³⁹ See PPLPC018001139508; See also PDD1712900150.

⁹⁴⁰ See PURCHI-000122070; See also PURCHI-000241775; See also JAN-MS-01466935.

⁹⁴¹ JAN-MS-00771526 at 3.

⁹⁴² JAN-MS-00771526 at 31.

OxyContin/oxycodone with regards to abuse liability and withdrawal, even though as noted above FDA had found that Nucynta had a safety profile similar to other opioids.

450. For example, Janssen's pre-launch 2008 Business Plan for Tapentadol contained a "Brand Vision" slide which noted "Less withdrawal symptoms" under "Ease of Management (especially PCPs)." ⁹⁴³

451. Janssen's April 2009 "Market Overview Strategic Plan," dating just prior to the start of sales of Nucynta IR, also identified less withdrawal as a key marketing message.

451.1. A slide asserting that "Under-Management Driven by Side Effects" led to the "Severe Consequences" of acute pain becoming chronic depicted tapentadol as having less withdrawal and "dose creep." ⁹⁴⁴

451.2. "Less withdrawal symptoms" is also identified on a slide entitled "Tapentadol Value Proposition." ⁹⁴⁵

451.3. Another slide identifies "Fewer withdrawal symptoms vs oxycodone upon abrupt discontinuation" among "PCP Relevant Outcomes." ⁹⁴⁶

451.4. In a slide with a "Reasons to Believe" exercise, "Demonstrates fewer and milder withdrawal effects than oxycodone" is identified as a "Brand Lifting" statement that is among the "Key Features to Keep in Messaging." ⁹⁴⁷

451.5. "Withdrawal" is also listed as a factor that is "Critical to [Nucynta] ER formulation VP [Value Proposition]." ⁹⁴⁸

⁹⁴³ JAN-MS-00443233 at 12.

⁹⁴⁴ JAN-MS-00457581 at slide 9.

⁹⁴⁵ JAN-MS-00457581 at 10.

⁹⁴⁶ JAN-MS-00457581 at 41.

⁹⁴⁷ JAN-MS-00457581 at 92.

⁹⁴⁸ JAN-MS-00457581 at 118.

451.6. Nowhere in the slides above is it noted that, as found by FDA in review of Nucynta IR's NDA, lower withdrawal with Nucynta IR was noted using only one opioid withdrawal scale in one study against one comparator opioid (oxycodone), or that another opioid withdrawal scale utilized in the same study did not find meaningfully lower withdrawal compared to oxycodone.⁹⁴⁹ In addition, as noted above, FDA found in its MOR of Nucynta ER that it had dependence/withdrawal characteristics similar to other long acting opioids.⁹⁵⁰ I can find no evidence in the record that Janssen obtained FDA approval to make a superiority claim on the label of Nucynta IR or ER of less withdrawal than oxycodone or any other opioid.

452. Janssen's Tapentadol Global Commercial Team PowerPoint dated April 15, 2009, shortly before sales of Nucynta IR began, included the following slides about addiction concerns:

452.1. A slide on "Current Treatment Dynamics" showing "Fear of Addiction and abuse" leading to "Inadequate management of acute pain," for which Tapentadol would be a solution.⁹⁵¹

452.2. A slide entitled "Opiophobia," showing "Fear of addiction" leading to "Myths" and "Fear of diversion," in turn leading to "Fears preclude patient validation of true pain."⁹⁵²

452.3. A slide entitled "Market Dynamics—Barriers," listing "Fear of addiction" and "Entrenchment of Oxycodone."⁹⁵³

⁹⁴⁹ Center for Drug Evaluation and Research, APPLICATION NUMBER:22-304, MEDICAL REVIEW(S), Part 2. at 71, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022304s000_MedR_P2.pdf (last visited March 20, 2019), FDA Medical Officer Review for Tapentadol, January 23, 2008, at 72, 153.

⁹⁵⁰ *Id.*

⁹⁵¹ JAN-MS-00457581 at 12.

⁹⁵² JAN-MS-00457581 at 69.

452.4. A slide entitled “Tapentadol Brand Map,” listing under “Unmet Needs” “Efficacy of oxycodone without the baggage.”⁹⁵⁴

453. Similarly, launch plans for Nucynta ER indicated the importance of concerns about abuse, and the ability to distinguish Nucynta with regards to abuse, to Janssen’s plans to market the drug:

453.1. A 2011 Draft Nucynta Business Plan dated July 27, 2010 asked on a slide entitled “Key Business Questions: Tapentadol ER:” “Can tapentadol ER demonstrate lower abuse potential?”⁹⁵⁵

453.2. Another slide in this 2010 PowerPoint entitled “Strategies & Executional Drivers” listed several comparisons of Nucynta ER to “oxy” under “Strengthen differentiation,” including “reduced abuse potential.”⁹⁵⁶

453.3. A slide regarding “Key Prescriber Insights” on Nucynta noted that a “Driver” for Primary Care was “low perceived addiction and/or abuse potential.”⁹⁵⁷

453.4. A slide listing “2011 Opportunities,” includes “OxyContin fatigue w/payers/Purdue irresponsibility.”⁹⁵⁸

453.5. In a July 21, 2011 “Promotional Platform: Physicians & Payers” PowerPoint addressing the launch of Nucynta ER, Janssen observed that “Abuse and misuse [are] cited as key issues” in the U.S. long-acting opioid market.⁹⁵⁹

⁹⁵³ JAN-MS-00457581 at 76.

⁹⁵⁴ JAN-MS-00457581 at 94.

⁹⁵⁵ JAN00008227 at 3.

⁹⁵⁶ JAN00008227 at 5.

⁹⁵⁷ JAN00008227 at 20.

⁹⁵⁸ JAN00008227 at 24.

⁹⁵⁹ JAN-MS-00010752 at 25.

453.6. Another slide in the 2011 PowerPoint listed “Less addiction/abuse potential” as the top “payer unmet need” in the U.S. long-acting opioid market.⁹⁶⁰ This item was circled and had a green check mark beside it for emphasis on the slide.

453.7. This point was reinforced by another slide in the same deck listing “Increased use of opioids is associated with increased abuse and diversion” as the highest priority challenge for MCOs [managed care organizations] and PBMs [pharmacy benefit managers].⁹⁶¹

454. A member of Janssen’s medical affairs team pushed back on proposed launch materials that sought to differentiate Nucynta with regards to abuse concerns. In January 2009, shortly after the approval of Nucynta IR and before sales of it had begun, Tanya Nelson, one of Janssen’s Senior Medical Science Liaisons, emailed a 19-bullet-point list of reasons that sections of proposed “Tapentadol 24 Hour Launch Training Workshop” videos needed to be rewritten. Included on the list was “we don’t have data supporting decreased abuse potential,” and “superiority claims in efficacy/safety can’t be made vs oxycodone.”⁹⁶²

455. At her deposition, Roxanne McGregor-Beck, a Johnson & Johnson Director of Regulatory, Advertising and Promotion, testified that she agreed with Nelson’s statement regarding the lack of data supporting decreased abuse potential claims, and noted “[I]t would be inconsistent with our label, and it would be very difficult for them to do so if there was no data to support [decreased abuse potential claims].”⁹⁶³ While Ms. Nelson later wrote that “approval of the workshops is contingent upon the corrections that need to be incorporated into these

⁹⁶⁰ JAN-MS-00010752 at 29.

⁹⁶¹ JAN-MS-00010752 at 42.

⁹⁶² JAN-MS-00469968.

⁹⁶³ Roxanne McGregor-Beck Dep., 57:1-16 (January 17, 2019).

materials,”⁹⁶⁴ I was unable to determine from the record whether her corrections were indeed made.

456. However, once Nucynta was on the market, Janssen continued to understate the risk of abuse by seeking to differentiate its drug as having lower abuse and withdrawal without substantial evidence, and by understating the risk of addiction from opioids in its unbranded advertising.

456.1. In Janssen’s 2012 Nucynta and Nucynta ER Business Plan, Janssen laid out a marketing strategy to “generate data to support lower abuse potential” in order to “strengthen differentiation and value through new & compelling evidence.”⁹⁶⁵

456.2. The 2012 Business Plan further identified “Lower Abuse Potential” as a “Strategic Driver” and proposed abuse potential studies, including a trial against OxyContin. Another slide in the Plan indicated that “Abuse Potential Trial Interim Results” would come in the Second Quarter of 2014.⁹⁶⁶ I can find no evidence in the record that such a trial took place, and Janssen sold Nucynta in early 2015.

456.3. The 2012 “Video Walk –Through” sales aid and script contained a screen shot with a header stating “Make NUCYNTA ER Your Choice for Chronic Pain” along with tabs including “Dual Mechanism of Action,” “Efficacy,” and “Tolerability/Safety/Withdrawal.” Notes underneath the screen shot state, “The low back pain study efficacy, the GI tolerability, and the withdrawal information continue to

⁹⁶⁴ JAN-MS-01124841.

⁹⁶⁵ JAN-MS-00010801 at 12, 42.

⁹⁶⁶ JAN-MS-00010801 at 43, 44.

be the crux of the NUCYTNA ER story, and you should keep reinforcing these critical messages.”⁹⁶⁷

456.4. A SWOT analysis in the 2012 Business Plan, identified among the drug’s strengths “Perceived lower abuse potential for Nucynta? (actionable?).”⁹⁶⁸

456.5. In Janssen’s 2013 Preliminary Business Plan for Nucynta IR and ER, Janssen again put forth “Generate data on comparative effectiveness, efficiency and abuse” as a differentiation strategy.⁹⁶⁹ There is still no indication a comparative study was yet underway.

456.6. In May 2013, despite the fact that the Nucynta ER had not been approved as tamper resistant, Janssen instructed its sales representatives, if asked by customers whether Nucynta was tamper resistant or abuse deterrent, to respond that “The NUCYNTA ER formulation was designed to not be amenable to splitting, crushing, or dissolution,” while also noting that the ability of Nucynta ER “to deter abuse, misuse, or diversion has not yet been established.”⁹⁷⁰

456.7. In a document entitled, “Pain Force District Manager’s meetings with Pharmacy District/Regional Directors” from September 2013, shortly after FDA denied Janssen’s request for TRF labeling, Janssen provided its district managers with a list of Do’s and Don’ts. Under “Don’t,” Janssen advised its sales team, “Don’t: Discuss topics concerning abuse, misuse, and diversion.”⁹⁷¹

⁹⁶⁷ JAN-MS-00774016 at 6.

⁹⁶⁸ JAN-MS-00010801 at 61.

⁹⁶⁹ JAN-MS-00011318 at 7.

⁹⁷⁰ JAN-MS-00658451; JAN-MS-00658452.

⁹⁷¹ JAN-MS-00982914.

456.8. In its 2014 Pain Business Review for Nucynta IR and ER, Janssen claimed that “NUCYNTA ER differentiated on Tolerability and Abuse Potential relative to competition.”⁹⁷²

456.9. The Pain Business Review contained a “NUCYNTA ER Positioning Statement” asserting that Nucynta “offers a superior overall clinical profile because: it provides best-in-class efficacy across multiple pain types... so that: physicians and patients can achieve their individualized pain improvement goals without many of the challenges typically associated with traditional opioids.”⁹⁷³

456.10. Despite the fact that by this time FDA had denied Janssen's request for TRF labeling for Nucynta ER, as noted above, the Pain Business Review identified among the “RTBs [reasons to believe]” for the Positioning Statement the following: “Uses technology designed to make it more difficult to crush, split, and dissolve.”⁹⁷⁴

456.11. From 2013 to 2015, there were 24 sales calls/visits for Nucynta ER that had “withdrawal” included in the key message.⁹⁷⁵

457. Janssen also understated the risk of addiction and withdrawal from opioids in its unbranded website, prescriberresponsibly.com.

457.1. A piece on the website entitled “Use of Opioid Analgesics in Pain Management,” by Keith Candiotti, downplayed the risk of addiction, stating as follows:

Aside from medical issues related to opioid analgesics, there are nonmedical issues that may have an impact on prescribing patterns and patient use of these drugs. Practitioners are often concerned about

⁹⁷² JAN-MS-02389698 at 23.

⁹⁷³ JAN-MS-02389698 at 73.

⁹⁷⁴ JAN-MS-02389698 at 74.

⁹⁷⁵ JAN00118960. No narrative is provided for these call notes so the exact nature of what was discussed is unknown.

prescribing opioid analgesics due to potential legal issues and questions of addiction. By the same token, patients report similar concerns about developing an addiction to opioid analgesics. While these concerns are not without some merit, it would appear that they are often overestimated. According to clinical opinion polls, true addiction occurs only in a small percentage of patients with chronic pain who receive chronic opioid analgesics analgesic therapy.⁹⁷⁶

457.2. A number of materials posted on the website minimized the risk of addiction by invoking the concept of pseudoaddiction. For example, in a piece entitled “What a Prescriber Should Know Before Writing the First Prescription,” Heit & Gourlay defined pseudoaddiction as “a syndrome that causes patients to seek additional medications due to inadequate pharmacotherapy being prescribed. Typically when the pain is treated appropriately, the inappropriate behavior ceases.”⁹⁷⁷

458. Janssen also financially supported and worked with pain advocacy organizations that put forth “educational” materials and activities that falsely claimed that the risk of opioid addiction had been exaggerated. Below is a brief summary of Janssen’s involvement in these advocacy organizations and their false and misleading statements:

458.1. From January 2012 through March 2017 Janssen spent \$465,152.85 funding seven different pain advocacy groups.⁹⁷⁸ Those groups are: Academy of Integrative Pain Management, American Academy of Pain Management, American

⁹⁷⁶ *Id.*

⁹⁷⁷ JAN-MS-03090578.

⁹⁷⁸ Fueling an Epidemic: Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups. U.S. Senate Homeland Security & Governmental Affairs Committee, Ranking Member’s Office, PPLPC031001561047 at 5. Also available at <https://www.hsgac.senate.gov/imo/media/doc/REPORT-Fueling%20an%20Epidemic-Exposing%20the%20Financial%20Ties%20Between%20Opioid%20Manufacturers%20and%20Third%20Party%20Advocacy%20Groups.pdf>

Chronic Pain Association, American Pain Society, American Society of Pain Management Nursing, The Center for Practical Bioethics, and U.S Pain Foundation.

458.2. The “Marketing Overview Strategic Plan” discussed above shows that Janssen worked with the American Pain Society to “Kick Off Unbranded Campaign” for its Nucynta launch in 2008, and sponsored an APS booth featuring a number of unbranded posters promoting Nucynta.⁹⁷⁹

459. In August, 2007, Will Rowe, the Executive Director of the American Pain Society, wrote to Greg Panico, a Janssen Executive, about APS’s efforts to push back against news stories about abuse and diversion of opioids.

459.1. The email stated:

As you know, the recent AP story about the DEA figures regarding the prescription and use of opioid medicines received wide and, in many cases poorly slanted coverage. The day after the AP release we received a call from NBC News wanting to get our reaction to the AP story. They seemed headed to report in a similar direction fanning concern that there were too many opioid medicines out there causing havoc in the nation. We talked with them extensively about the other side of the story and had them speak to two pain patients and a pain physician.⁹⁸⁰

459.2. Mr. Panico forwarded Mr. Rowe’s email on to other Janssen employees, describing it as “a surprisingly balanced story that addresses value of opioids in treating chronic pain, including statement from Dr. Pamela Palmer at U California that opioids are chemicals like any other medicine and should not have stigma. APF seems to be a strong influencer of positive media coverage of this topic.”⁹⁸¹

⁹⁷⁹ JAN-MS-00457581 at 125.

⁹⁸⁰ JAN-MS-00275814.

⁹⁸¹ *Id.*

459.3. Mr. Panico also asked Ketchum for a copy of the article “to be able to use it at team PR update for tapentadol to show them that there is balanced coverage of this topic.”⁹⁸²

460. In my opinion, Janssen’s promotion of Nucynta misleadingly minimized the risks of abuse and addiction.

VIII. TEVA

A. Overview

461. Teva manufactures and markets various opioid products, including Actiq and Fentora.⁹⁸³

462. Actiq and Fentora are similar products. Both contain fentanyl,⁹⁸⁴ a known *mu*-opioid receptor agonist, and both are considered oral transmucosal fentanyl products.⁹⁸⁵

According to FDA, “Actiq is a lozenge that is presented on a stick making it easily removable from the mouth, while Fentora is a lozenge without a stick.”⁹⁸⁶

463. According to a 2008 FDA memorandum, approval of Actiq and Fentora “represented availability of fentanyl without the necessity of intravenous access.” Accordingly, “FDA had numerous discussions with the sponsors during the development of the products to

⁹⁸² *Id.*

⁹⁸³ The drug sponsor for Actiq was Anesta Corporation, which Cephalon, Inc. acquired in 2000. The drug sponsor for Fentora was Cephalon. Teva acquired Cephalon in 2009. These entities are referred to herein as “Teva.”

⁹⁸⁴ According to the DEA, “Fentanyl is a synthetic opioid that is 80-100 times stronger than morphine.” Available at <https://www.dea.gov/factsheets/fentanyl> (last visited March 25, 2019)

⁹⁸⁵ Oral transmucosal delivery allows for rapid onset of action to occur in less than hour. Actiq FDA Label, December 2016, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020747s043s0441bl.pdf (last visited March 25, 2019); Fentora FDA Label, December 2016. *available at*, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021947s024s0251bl.pdf (available at March 25, 2019)

⁹⁸⁶ PPLP004041768 at 2.

address our [FDA's] concerns regarding the potential for abuse and misuse, and the potential for accidental exposure with these formulations.”⁹⁸⁷

464. To minimize these concerns, “rigorous risk management programs were included as part of the approval of the products” that “were designed to limit the prescribing of these products to opioid tolerant patients with breakthrough pain from cancer with the intent that this would limit the overall prescribing of the medication.”

465. Teva's marketing of Actiq and Fentora ignored strict limitations imposed by FDA, as discussed below.

B. Actiq

1. Approval of Actiq for Limited Use.

466. FDA approved Actiq on November 4, 1998 for the limited indication of “management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.”⁹⁸⁸

467. On February 7, 2007, FDA approved a supplemental NDA, expanding the indication to “only for management of breakthrough cancer pain in patients 16 and older with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.”⁹⁸⁹ The revised label also included pharmacokinetic data on patients from ages 5 to 15, and stated that “safety and efficacy below age 16 years have not been established.”⁹⁹⁰

⁹⁸⁷ TEVA_MDL_A_02186676 at 1.

⁹⁸⁸ https://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/20747ltr.pdf at 5.

⁹⁸⁹ https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/020747s027ltr.pdf at 1.

⁹⁹⁰ https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020747s027lbl.pdf at 1.

468. FDA further required Actiq be “marketed in accordance with the terms of restricted distribution and use described in the Risk Management Program ..., and as recommended in the attached final labeling”⁹⁹¹

2. Teva Marketed Actiq for Non-Malignant Pain, for Which Safety Had Not Been Established by Substantial Evidence.

469. As noted above, Teva’s approved indication limited its use to only breakthrough pain among opioid tolerant patients with malignancies.

470. Teva acknowledged that Actiq’s narrow indication limited its marketability.

470.1. Upon acquiring the rights to Actiq in 2000, Teva reevaluated the business model and promotional activities for the product, issuing a “Master Plan” for Actiq on November 16, 2000 that included the following observation:

From its initial submission, through the approval process, and in the post marketing period, Actiq has been scrutinized especially closely by FDA. The impact is felt most acutely when comparing Actiq claims versus those that our competitors are allowed to make. This comparison leads us to believe that Actiq is currently competing on an “unlevel” playing field, and that a complete examination of our regulatory strategy should be undertaken.⁹⁹²

470.2. In this “Master Plan,” Teva likewise recognized Actiq’s narrow indication, remarking:

This is the very first time than an analgesic has ever been so tightly restricted in terms of a very specific type of pain (breakthrough cancer pain) in a very specific patient population (opioid tolerant patients with malignancies).[...]By the [FDA’s] own admission, these restrictions were established for social considerations and were not derived from any clinical experience.⁹⁹³

⁹⁹¹ TEVA_MDL_A_08242688 at 1.

⁹⁹² TEVA_CHI_00042757 at 40.

⁹⁹³ TEVA_CHI_00042757 at 40.

471. Despite acknowledging Actiq’s narrow indication, Teva developed marketing plans to expand the use of Actiq for non-malignant chronic pain:

471.1. For example, a key strategic recommendation of Teva’s 2000 “Master Plan” included expanding beyond cancer pain to chronic pain, noting “we believe it can continue to grow aggressively into 2001 and beyond by expanding the target physician and patient population to allow penetration of the broad chronic pain market.”⁹⁹⁴ In addition, Teva planned to target pain specialists rather than oncologists as pain specialists are “likely to be a more aggressive writer and rapid adopter of *Actiq*” and these physicians “tend to have patients that are more likely to be truly chronic, with many years of potential usage of the product, either for breakthrough pain **or more generally for other chronic pain conditions.**”⁹⁹⁵

471.2. In Teva’s 2003 Marketing Plan, a key marketing initiative was to increase the awareness of general breakthrough pain—or “BTP” as referred to by Teva—beyond that of the more narrow breakthrough cancer pain market—or “BTCP” market:

Many of our targeted physicians and healthcare providers (e.g., RNs, RPhs) believe that they are managing chronic pain adequately, despite the fact that most pain assessment tools do not include questions or pain scales specific to BTP. BTP must become recognized as a critical component of chronic pain that must be assessed and treated as distinct and separate entity from persistent pain.⁹⁹⁶

471.3. Teva’s 2003 Marketing Plan further noted that “anesthesiologists and other pain specialists who have similar prescribing habits, may not require substantial clinical evidence to implement ACTIQ in numerous disease states **other than**

⁹⁹⁴ TEVA_CHI_00042757 at 5.

⁹⁹⁵ TEVA_CHI_00042757 at 4 (emphasis added).

⁹⁹⁶ TEVA_CHI_00042882 at 39; *see also* TEVA_CHI_00042951 at 32.

BTCP...,⁹⁹⁷ adding that “the disease states that represent the largest growth opportunities for ACTIQ include, but are not limited to osteoarthritis, rheumatoid arthritis, chronic back pain, migraine headaches, complex regional pain syndrome and postherpetic neuralgia. Medical affairs support describing the rationale for a rapid acting opioid would help to drive these uses.”⁹⁹⁸

471.4. Teva’s 2003 Marketing Plan also identified strategies to “develop/renew relationships with KOL in the field of pain management in order for ACTIQ to gain the exposure and support needed to become a first line treatment option for BTP **in both malignant and non-malignant pain.**”⁹⁹⁹

471.5. Teva’s 2004 Marketing Plan identified similar strategies to those described in Teva’s 2003 Marketing Plan.¹⁰⁰⁰

472. Beginning as early as 2001, Teva was informed that Actiq was being prescribed for non-malignant breakthrough pain.

472.1. In May and December of 2001, Teva conducted tracking studies to determine how its product was being used.¹⁰⁰¹ The research found that pain specialists were using Actiq in a wide variety of disease states besides cancer, including lower back pain, osteoarthritis, reflex sympathetic dystrophy, post-trauma, fibromyalgia, adhesions, arachnoiditis, rheumatoid arthritis, and other types of headaches.¹⁰⁰²

⁹⁹⁷ TEVA_CHI_00042882 at 17 (emphasis added).

⁹⁹⁸ TEVA_CHI_00042882 at 17.

⁹⁹⁹ TEVA_CHI_00042882 at 39 (emphasis added).

¹⁰⁰⁰ TEVA_CHI_00042951.

¹⁰⁰¹ TEVA_CHI_00042882 at 15.

¹⁰⁰² TEVA_CHI_00042882 at 16.

472.2. In Teva's 2005 Marketing Plan, Teva reported that "[b]ased on physician reporting, 90% of ACTIQ use is for BTP **outside of cancer**, with the majority of use (55% of total) being for chronic back pain."¹⁰⁰³

472.3. Also in this marking plan, Teva included the chart below of Actiq use by specialty, noting that "specialty usage tends to fluctuate based on patient presentation and physician recognition of the need for rapid acting or BTCP/BTP. For example, neurology usage tends to be higher for headache (97%) while PCP usage is higher for back pain (81 %)."¹⁰⁰⁴

ACTIQ Use by Specialty[^]

	Anes / Pain	Neuro	PCP	Other	Total
Malignant pain	13%	6%	4%	35%	10%
Back pain	49%	21%	81%	41%	55%
Headache	17%	97%	19%	14%	22%
FMS / MPS *	14%	11%	17%	18%	18%
Arthritis	12%	7%	21%	8%	13%
CRPS **	9%	2%	5%	5%	7%
Neuropathy	10%	9%	21%	12%	12%

472.4. By 2006, chronic back pain represented 38% of the underlying conditions treated with Actiq, while cancer was only 8%.¹⁰⁰⁵

473. Following implementation of Teva's marketing plans, Teva's sales of Actiq increased:

473.1. Actiq's total prescriptions increased substantially each year from 1999 to 2003.¹⁰⁰⁶ Prescriptions in 1999 totaled 5,548 and had increased to 326,078 by 2003.¹⁰⁰⁷

¹⁰⁰³ TEVA_CHI_00043010 at 26 (emphasis added).

¹⁰⁰⁴ TEVA_CHI_00043010 at 26.

¹⁰⁰⁵ TEVA_CHI_00043963 at 51.

473.2. Factory sales of Actiq increased from \$1.8 million in the first quarter of 2000 to \$30.1 million by the second quarter of 2002.¹⁰⁰⁸ By the third quarter of 2004 factory sales had increased to over \$107 million.¹⁰⁰⁹

473.3. Actiq's sales continued to grow with sales totaling \$590.7 million in 2006.¹⁰¹⁰ By 2006 the price had increased to approximately \$1,863.¹⁰¹¹

473.4. The number of Actiq prescribers also increased during in this same time period from 26,200 prescribers in 2000 to 471,068 by 2005.¹⁰¹²

474. In my opinion, Teva marketed Actiq for non-cancer pain, an indication that lacked substantial evidence to support safety.

3. Teva Failed to Comply with its Risk Management Strategies in Marketing Actiq

475. FDA considered the Actiq RiskMap an “integral part of the approved NDA...and is an essential component of the terms of this NDA’s approval by FDA for marketing...”¹⁰¹³ The purpose of the RiskMap was “to ensure the safe use” of Actiq, and “[r]edundancy of the program elements is one measure used to strengthen the effectiveness of the [RiskMap].”¹⁰¹⁴

476. The FDA-mandated RiskMap required the dissemination of “key messages” on “Proper Patient Selection,” including “Actiq is specifically indicated solely for the treatment of

¹⁰⁰⁶ TEVA_CHI_00043010 at 11.

¹⁰⁰⁷ TEVA_CHI_00043010 at 11.

¹⁰⁰⁸ TEVA_CHI_00042882 at 6.

¹⁰⁰⁹ TEVA_CHI_00043010 at 9.

¹⁰¹⁰ TEVA_CHI_00043963 at 45.

¹⁰¹¹ TEVA_CHI_00043963 at 46.

¹⁰¹² TEVA_CHI_00043963 at 47.

¹⁰¹³ Actiq Approval Letter, November 4, 1998
https://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/20747ltr.pdf at 2.

¹⁰¹⁴ TEVA_MDL-A-03272088 at 5.

breakthrough cancer pain in chronic opioid tolerant cancer patients,” and on “Prevention of Diversion and Abuse Messages,” including “Actiq may be habit forming.”¹⁰¹⁵ The RMP also included a section on “Professional Medical Education” to deliver safety information and convey the key messages.¹⁰¹⁶

477. The FDA-mandated RiskMap included surveillance and monitoring programs that were designed to “determine the effectiveness of the Actiq Risk Management Program by monitoring [...] potential product use among opioid-non-tolerant populations [...] off-label use [...] and trigger intervention when problems are discovered.”¹⁰¹⁷

478. Teva was further required to “provide a quarterly report to the FDA compiled from all data collected by the methods described under the Actiq Surveillance and Monitoring Program and Interventions. This report will describe and provide data on any concerns for [...] off-label usage.”¹⁰¹⁸

479. As discussed above, Teva’s off-label marketing was contrary to the key messages in the FDA mandated RiskMap concerning proper patient selection and risks of abuse. Moreover, Teva was in possession of voluminous data and information indicating off-label use of Actiq. Rather than intervene and report to FDA, as required by its Risk Management Program, Teva embraced this inappropriate usage or looked the other way.

480. On December 2, 2003, an internal audit with the objective to “audit Actiq Risk Management Program reporting activities to determine compliance with filing requirements”

¹⁰¹⁵ TEVA_MDL_A_03272088 at 6.

¹⁰¹⁶ TEVA_MDL_A_03272088 at 12.

¹⁰¹⁷ TEVA_CHI_00049296 at 22.

¹⁰¹⁸ TEVA_CHI_00049296 at 29.

concluded that “based on the findings of this audit [...] Cephalon is not in compliance with the commitments communicated in the Risk Management Program dated August 1, 2001...”¹⁰¹⁹

481. Afterwards, Teva submitted a supplemental application seeking to change the Actiq RiskMap, which FDA found non-approvable on June 21, 2005.¹⁰²⁰ FDA found that Teva’s proposed changes would “decrease the surveillance of off-label use of Actiq in the face of increasing off-label use by prescribers,” and required that Cephalon “Justify the proposal for decreased monitoring of off-label use of Actiq, and outline effective interventions to discourage it.”¹⁰²¹ Teva never justified its proposal to decrease monitoring for off-label use to FDA, and so no further changes to the Actiq RiskMap were approved.

482. In my opinion, Teva failed to comply with its risk management obligations in marketing Actiq.

C. Fentora

1. Approval of Fentora for Limited Use.

483. The FDA approved Fentora (fentanyl buccal tablet), manufactured by Teva, on September 25, 2006.¹⁰²²

484. Fentora was approved for the “management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.”¹⁰²³ Unlike Actiq, Fentora did not have distribution restrictions placed upon it at approval.

¹⁰¹⁹ TEVA_MDL_A_01159585 at 1

¹⁰²⁰ TEVA_MDL_A_01583458 at 1.

¹⁰²¹ TEVA_MDL_A_01583458 at 1.

¹⁰²² https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021947s000ltr.pdf. The FDA approved Fentora for five dosage strengths, 100, 200, 400, 600, and 900 mcg.

¹⁰²³ https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021947s000ltr.pdf.

2. Teva Promoted Fentora for Non-Malignant Pain, for which it Lacked Substantial Evidence to Support Safety

485. Like Actiq, Fentora had a very narrow labeled indication.

486. Notwithstanding this narrow indication, and the off-label use of Actiq, Teva identified “convert ACTIQ loyalists to FEBT adopters” as a “critical success factor” for Fentora.¹⁰²⁴

487. In its December 2005 Fentora Marketing Plan, Teva stated it planned to convert Actiq loyalists by “leveraging strong relationships and bridging from the solid market conditioning base it established prelaunch.”¹⁰²⁵

488. Teva continued to use the strategy developed for Actiq, specifically continuing to expand the usage of Fentora beyond the appropriate use in break through cancer pain – referred to as BTCP – to off-label use in the broader break through pain – referred to as BTP – market.

489. The 2005 Marketing Plan stated that a “critical success factor” identified for Fentora was to encourage off label use in non-cancer break through pain (BTP), specifically by “continu[ing] to develop BTP market by increasing awareness and understanding of BTP and its optimal treatment.”¹⁰²⁶

490. Like with Actiq, Teva was successful in encouraging off-label use in non-cancer patients. According to a July 2, 2008, Fentora Marketing Overview presentation, by 2007, of approximately 22,000 patients treated with Fentora, cancer patients represented only 18%.¹⁰²⁷

¹⁰²⁴ TEVA_MDL_A_00368405 at 6, 15.

¹⁰²⁵ TEVA_MDL_A_00368405 at 12.

¹⁰²⁶ TEVA_MDL_A_00368405 at 14

¹⁰²⁷ TEVA_MDL_A_01500140 at 41.

“Other pain” was the most frequently treated underlying condition (27%) followed by back pain (20%) and other diagnosis (20%).¹⁰²⁸

491. The same July 2008 marketing presentation reported that in July 2007 pain specialists were writing the most Fentora prescriptions (49%), followed by primary care physicians (22%), and other physicians (20%).¹⁰²⁹ Oncologists wrote only 3% of the prescriptions.¹⁰³⁰ In May 2008, there was a slight decrease in prescribing pain specialists (47%), and an increase in primary care prescribers (23%).¹⁰³¹

492. From September 2007 to December 2008, pain specialists continued to write the most Fentora prescriptions (44%), followed by primary care physicians (21%).¹⁰³² Oncologists continued to rarely write Fentora prescriptions (3%).¹⁰³³ During this time there was an overall decrease in the number of pain specialists prescribing Fentora on a monthly basis.¹⁰³⁴

493. In my opinion, Teva promoted Fentora for non-malignant pain, which lacked substantial evidence to support safety.

¹⁰²⁸ TEVA_MDL_A_01500140 at 41.

¹⁰²⁹ TEVA_MDL_A_01500140 at 59.

¹⁰³⁰ TEVA_MDL_A_01500140 at 59.

¹⁰³¹ TEVA_MDL_A_01500140 at 60.

¹⁰³² TEVA_MDL_A_00398245 at 31.

¹⁰³³ TEVA_MDL_A_00398245 at 31.

¹⁰³⁴ TEVA_MDL_A_00398245 at 31.

IX. ACTAVIS

A. Overview

494. Kadian is the brand name for extended-release oral formulation of morphine sulfate, an opioid analgesic with a release rate-controlling polymer coating marketed by Actavis.¹⁰³⁵

495. The FDA approved Kadian on July 26, 1996 “for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.”¹⁰³⁶

496. Kadian capsules “share the risks of other prescription opioids.”¹⁰³⁷

B. Actavis Promoted Kadian in a Manner that Understated Its Risks, Overstated Its Benefits, and for Indications that Lacked Substantial Evidence to Support Safety and Efficacy.

497. Actavis recognized that “the market for both acute and chronic pain medications [was] increasing, [and] that the chronic pain segment had experienced [] dramatic growth.”¹⁰³⁸

498. The Kadian marketing plan took into account that “over half of the people taking prescription pain medication or over-the-counter drugs [were] NOT satisfied with their current treatment plan,” and that this presented “a significant marketing opportunity for the right drug in the chronic pain market.”¹⁰³⁹

¹⁰³⁵ ALLERGAN_MDL_0007776; ACTAVIS0248829. Actavis acquired Kadian from Alpharma on December 19, 2009 and began marketing it on or around that date. ALLERGAN_MDL_01514893. The specific entities that held the Kadian NDA were: Actavis Elizabeth LLC (December 2008-2013); Actavis Laboratories UT, Inc. f/k/a Watson Laboratories, Inc. – Salt Lake City (2013-2016); and Allergan Sales, LLC (2016-present). Allergan-Kaufhold-003 at 6.

¹⁰³⁶ ACTAVIS0248829 at 1. The Kadian dosages available since introduction have varied, but have included 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, 130 mg, 150 mg, and 200 mg of morphine sulfate. ALLERGAN_MDL_0007774.

¹⁰³⁷ ACTAVIS0248829 at 1.

¹⁰³⁸ ACTAVIS00006930 at 11.

¹⁰³⁹ ACTAVIS00006930 at 11 (emphasis in original).

1. Actavis Promoted Kadian for Indications Broader than Supported by Substantial Evidence and for Which Safety and Efficacy Were Not Established.

499. On February 18, 2010, Actavis received a Warning Letter from DDMAC concerning Actavis's promotional launch materials for Kadian, which included a Co-Pay Assistance Program Brochure and a "PK to PK Comparison Detailer" for Kadian.¹⁰⁴⁰

500. Kadian's PK to PK Comparison Detailer, included the following claims:

- **"Allows for less breakthrough pain and more consistent pain relief for patients"**
- **"Better pain control"**
- **"Allow patients to live in less pain"**
- **"Allow individualization and customization of a patient's pain treatment"**
- **"Prescribe KADIAN – Less pain for your patients. More options for you."**
- **"Less Pain. More Options."**¹⁰⁴¹

501. Similarly, Kadian's Co-Pay Brochure included the following statements:

- **"Why is pain management important?** Pain management is a large part of your overall health care plan. Many Americans suffer from chronic or ongoing pain . . . Managing your pain the right way begins by talking to your healthcare provider. Discover the cause of your pain by taking note of what makes your pain start and what makes it worse."
- **"What is chronic pain?** Chronic pain is ongoing and can last longer than 6 months. Chronic pain can be mild or severe"
- **"How can I treat my chronic pain?** To help manage your pain, your healthcare provider will chose a drug that works just for you."¹⁰⁴²

502. According to FDA, these promotional materials suggested that Kadian would be appropriate for use in broader types of pain than indicated.¹⁰⁴³ FDA found these presentations

¹⁰⁴⁰ ACTAVIS0238310 at 1.

¹⁰⁴¹ ACTAVIS0238310 at 5.

¹⁰⁴² ACTAVIS0238310 at 6.

“particularly concerning considering the serious and potentially fatal risks associated with the drug,” and emphasized that “Kadian is only appropriate for a very limited patient population who experience pain.”¹⁰⁴⁴

503. FDA likewise found that both promotional pieces provided only a partial indication for Kadian, omitting the important limitation that:

KADIAN is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time. KADIAN is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate ...¹⁰⁴⁵

504. FDA noted that “the statement, ‘*Please see accompanying complete Prescriber Information*’ [which] appears on various pages of the Comparison Detailer and Co-Pay [Brochure] . . . does not mitigate the implications [these] claims and presentations.”¹⁰⁴⁶

505. Despite FDA’s warning that Actavis should refrain from marketing Kadian for use in broader populations than indicated, Actavis used promotional messages similar to those described.

505.1. For example, Actavis’s sales training for Kadian included a general and expansive definition of pain that was not focused on the “moderate to severe” pain threshold that Kadian was intended to treat.¹⁰⁴⁷ The sales training materials appear to have been in continuous use until at least 2013.¹⁰⁴⁸

¹⁰⁴³ *Id.*

¹⁰⁴⁴ *Id.*

¹⁰⁴⁵ *Id.*

¹⁰⁴⁶ *Id.* (emphasis in original).

¹⁰⁴⁷ ALLERGAN_MDL_01610522 at 8.

¹⁰⁴⁸ See ALLERGAN_MDL_01610520 (indicating date and circulating Kadian Training Manual);

505.2. The misleading messaging identified in FDA's warning letter was used by Actavis both in the sales training materials and the marketing materials at issue in the DDMAC letter.¹⁰⁴⁹

506. In my opinion, Actavis promoted Kadian for indications broader than supported by substantial evidence and for which safety and efficacy were not established.

2. Actavis Overstated the Benefits of Kadian with Respect to Functionality and Quality of Life.

507. The Co-Pay Brochure that Actavis used for promotion of Kadian included the following presentations:

- “. . . Many Americans suffer from chronic or ongoing pain. It can cause you to miss work and can even keep you from enjoying life. If left untreated pain can place stress on your body and your mental health. . . .”
- “. . . Chronic pain . . . can be inconvenient and can keep you from your daily tasks.”¹⁰⁵⁰

508. As indicated in the DDMAC Letter above, FDA found that these representations constituted unsubstantiated effectiveness claims, explaining that it is “not aware of substantial evidence or substantial clinical experience demonstrating that the magnitude of the effect the drug has in alleviating pain, taken together with any drug-related side effects patients may experience (such as the common adverse events of drowsiness, dizziness, constipation and nausea) results in an overall positive impact on a patient's work, physical and mental functioning, daily activities, or the enjoyment of life.”¹⁰⁵¹

¹⁰⁴⁹ See ALLERGAN_MDL_01234652.

¹⁰⁵⁰ ACTAVIS0238310 at 10.

¹⁰⁵¹ ACTAVIS0238310 at 11.

509. In addition, FDA noted it was “not aware of any studies demonstrating that the level of pain reduction experienced by patients on Kadian therapy corresponds with a positive impact on the outcomes claimed.”¹⁰⁵²

510. In my opinion, Actavis’s promotional materials overstated the benefits of Kadian with respect to patient functionality and quality of life.

(a) Actavis Falsely Marketed Kadian as Safer and More Effective than Other Opioid Products.

511. As indicated in the DDMAC Letter, Actavis’s Comparison Detailer misleadingly implies “that Kadian has been shown to be superior to MS Contin and generic controlled-release morphine because Kadian’s pharmacokinetic properties will lead to less to less breakthrough pain and more consistent pain relief.”¹⁰⁵³

512. Specifically, the Comparison Detailer includes the following claims:

- **“Why settle for generic MS Contin tablets . . . When you can prescribe the benefits of Kadian capsules?”**
- **“Fewer peaks and valleys
Smooth steady state plasma levels compared with controlled-release (CR) morphine tablets q12h and q24h.”**
- **“Allow for less breakthrough pain and more consistent pain relief for patients.”**

513. For support of the above claims, the Comparison Detailer cites to current Kadian prescribing information and to Geoffrey, *et. al.*, *Pharmacokinetics and pharmacodynamics of twenty-four-hourly Kapanol compared to twelve-hourly Ms Contin in the treatment of severe cancer pain*, 69 Pain 295–302 (1997).¹⁰⁵⁴ However, FDA stated it was not “aware of any

¹⁰⁵² *Id.*

¹⁰⁵³ ACTAVIS0238310 at 7.

¹⁰⁵⁴ *Id.*

substantial evidence or substantial clinical experience that supports these claims and presentations.”¹⁰⁵⁵

514. In addition, as the DDMAC Letter indicated, “the Comparison Detailer include[d] the following pain and sleep-related claims and presentations that compare[d] Kadian to MS Contin and generic controlled-release morphine:

- **‘Better pain control and improved sleep scores’**
- **‘Improved pain control and sleep scores in patients treated with KADIAN who were previously on CR morphine tables’**
- **‘Allow patients to live with less pain and get adequate rest with less medication’”¹⁰⁵⁶**

515. FDA found that Actavis supported these claims by citing to “a historically controlled study of inadequate design, completely lacking any concurrent control.”¹⁰⁵⁷ FDA reiterated that it was “not aware of any substantial evidence or substantial clinical experience to support such a claim.”¹⁰⁵⁸

516. FDA also noted that “the Comparison Detailer include[d] the following dosing claims and presentations that compare Kadian with both MS Contin and AVINZA (morphine sulfate extended-release capsules, CII (Avinza):

- **‘Fewer barriers to prescribing...[t]he unique dosing flexibility of KADIAN gives you more options with a morphine’**
- ‘Claims below the chart include the following:
 - **No immediate-release (IR) component**
 - **No ceiling dose – contains no acetaminophen, ibuprofen, or fumaric acid**
 - **Allows for titration in increments of 10 mg, with a low dose**

¹⁰⁵⁵ *Id.*

¹⁰⁵⁶ ACTAVIS238310 at 8 (emphasis in original).

¹⁰⁵⁷ ACTAVIS238310 at 9.

¹⁰⁵⁸ *Id.*

- of 10 mg
- **Allow individualization and customization of a patient’s pain treatment”**¹⁰⁵⁹

517. FDA further stated, “These claims are misleading because they imply that Kadian is superior to both MS Contin and Avinza because Kadian’s dosage strength...offers ‘fewer barriers to prescribing,’ and because Kadian has no immediate release component, no ceiling dose, and allows for 10 mg titration increments.”¹⁰⁶⁰ “FDA again noted that it was “unaware of any substantial evidence or substantial clinical experience to support the claim that the above dosing characteristics allow Kadian to have ‘fewer barriers to prescribing’ (the meaning of which is not clear) as compared to other extended-release morphine products.”¹⁰⁶¹

518. A training brochure used by the Actavis sales team as of December 14, 2009 made similar comparisons to those criticized as improper in the DDMAC letter.¹⁰⁶²

519. Actavis’s sales representatives were trained to make misleading statements, unsupported by substantial evidence, that Kadian had lower abuse potential as compared to other opioid products, including the following claims:

“KADIAN patients experience sustained morphine release with less fluctuations vs. morphine sulfate.”

“KADIAN patients report improved management of pain vs. morphine sulfate.”

¹⁰⁵⁹ ALLERGAN_MDL_00813589 at 4 (emphasis in original).

¹⁰⁶⁰ *Id.*

¹⁰⁶¹ *Id.*

¹⁰⁶² Compare ACTAVIS0799208 (criticizing the comparison “Fewer peaks and valleys” and comparison graphs) with ALLERGAN_MDL_01234657 (the same comparison); compare ACTAVIS0799209 (criticizing the comparison “Better pain control and sleep scores” and comparison graphs) with ALLERGAN_MDL_01234658 (the same comparison); compare ACTAVIS0799211 (criticizing the comparison “Fewer barriers to prescribing” and subsequent explanatory text) with ALLERGAN_MDL_01234656 (the same comparison and similar explanatory text).

“KADIAN patients require less rescue medication vs. morphine sulfate.”¹⁰⁶³

520. Even after receipt of the DDMAC letter, Actavis’s sales representatives continued to be trained to make misleading statements, unsupported by substantial evidence, that Kadian provided steady blood levels of morphine and “few peaks and valleys.”

389.1 A November 2011 sales team training PowerPoint trained Actavis’s sales representatives to utilize the statement that: “Kadian provides steady blood levels of morphine sulfate with few peaks and valleys.”¹⁰⁶⁴

389.2 March 2013 marketing sales training presentation instructed: “Kadian provides steady blood levels with few peaks and valleys (show PK charts from Detail Aid)”¹⁰⁶⁵

389.3 A February 2013 Kadian Sales Training Presentation stated: “Kadian provides steady blood levels of morphine sulfate with few peaks and valleys.”¹⁰⁶⁶

389.4 A September 13, 2012 Kadian Marketing Update likewise instructed: “Experience sustained morphine release with less fluctuations vs. morphine sulfate” “Report improved management of pain vs. morphine sulfate.

¹⁰⁶³ ALLERGAN_MDL_00020454 at 47.

¹⁰⁶⁴ ACTAVIS0335094 at 10.

¹⁰⁶⁵ ACTAVIS0000564 at 27 and 30.

¹⁰⁶⁶ ALLERGAN_MDL_00001525 at 21.

Require less rescue medication vs. morphine sulfate.”¹⁰⁶⁷ “Kadian provides steady blood levels of morphine sulfate with few peaks and valleys.”¹⁰⁶⁸

521. Actavis received reports that the message that Kadian had “low abuse potential” was delivered to prescribers:

382.1. A September 2011 Kadian Prescriber Research report from an in-depth blinded telephone interview conducted with 12 high volume prescribers of long-acting opioids stated that prescribers reported that Kadian’s strengths included its “low abuse potential.”¹⁰⁶⁹

382.2. “Among those interviewed, Kadian represent[ed] a leading choice of LAO therapy” and was “cited by several as the #1 choice” because of its “low abuse potential” among other reasons.¹⁰⁷⁰

382.3. A September 13, 2012 Kadian Marketing Update, similarly stated that “called-on physicians” reported a perception that Kadian had “low abuse potential.”¹⁰⁷¹

522. In my opinion, Actavis falsely marketed Kadian as safer and more effective than other opioid products.

(b) Actavis Misleadingly Promoted Kadian as Having No Alcohol-Induced Dose Dumping Effect.

523. In 2007, Actavis supported an open-label, in vivo study of the “interaction between Kadian and alcohol” “among 32 healthy male volunteers.”¹⁰⁷² The results of the study

¹⁰⁶⁷ ALLERGAN_MDL_00072907 at 5.

¹⁰⁶⁸ ALLERGAN_MDL_00405512 at 11.

¹⁰⁶⁹ ACTAVIS0268659 at 2-8.

¹⁰⁷⁰ ACTAVIS0268659 at 23

¹⁰⁷¹ ALLERGAN_MDL_00072907 at 3.

¹⁰⁷² ALLERGAN_MDL_01741520.

were presented in The Journal of Pain in April 2008, in an article titled *Effect of Concomitant Ingestion of Alcohol on the In Vivo Pharmacokinetics of KADIAN (Morphine Sulfate Extended Release) Capsules*.¹⁰⁷³

524. According to a summary prepared by Actavis, “[t]he study was undertaken in response to: [t]he withdrawal of Palladone (hydromorphone hydrochloride extended-release) from the market in 2005 after pharmacokinetic data revealed a risk of alcohol-induced dose-dumping” and “[r]ecommendation made by the FDA to further investigate the possibility that other sustained-release narcotics could pose the same danger as Palladone.”¹⁰⁷⁴

525. Actavis claimed that “Although it is recommended that alcohol not be used while the patient is taking opioids, results of this in vivo study indicate that the risk of alcohol-induced dose-dumping in connection with the use of KADIAN is negligible.”¹⁰⁷⁵

526. Actavis instructed its sales force to make promotional claims based on this single-open label study. A single open label study does not constitute substantial evidence in which to draw promotional claims.¹⁰⁷⁶ An Actavis summary of key talking points for the open-label study stated:

- KADIAN is the only extended release opioid product to have demonstrated in vivo that there is no dose dumping¹⁰⁷⁷ of morphine sulfate when taken with

¹⁰⁷³ *Id.*

¹⁰⁷⁴ ALLERGAN_MDL_00438794 at 1.

¹⁰⁷⁵ *Id.* at 11.

¹⁰⁷⁶ In promotion, treatment claims must generally be supported by “substantial evidence” or “two, adequate and well-controlled trials.” An open-label clinical trial is insufficient to satisfy this requirement. 21 U.S.C. § 355(d)(“‘substantial evidence’ means evidence consisting of adequate and well-controlled investigations...”)(emphasis added).

¹⁰⁷⁷ Dose-dumping “is the unintended, rapid release of a clinically-significant fraction of a drug substance from a modified-release formulation. Depending on the therapeutic index of a drug, dose-dumping can pose a significant risk to patients due to safety issues, diminished efficacy, or both. Generally, dose-dumping is due to a compromise of the mechanism that retards the rate of drug substance release from the formulation.” ALLERGAN_MDL_00947173 at 3.

alcohol”¹⁰⁷⁸

- “Other products (e.g., AVINZA, OPANA ER, EMBEDA) in the class carry serious warnings regarding concomitant use with alcohol”¹⁰⁷⁹
- “Although it is recommended that alcohol not be used while the patient is taking opioids, results of this in vivo study indicate that for patients requiring therapy for management of moderate to severe pain, in whom consumption of alcohol may occur, KADIAN may represent the safest choice”¹⁰⁸⁰

527. Actavis’s training materials also indicated that AVINZA, OPANA ER, and EMBEDA included Black Box warnings concerning alcohol consumption while KADIAN did not.¹⁰⁸¹

528. In an email dated October 15, 2009, Nathalie Leitch, Director, Specialty Rx at Actavis, indicated to Christine Balogh, Vice President Client Development at CHS consulting, and others that Actavis and its sales team “[were] looking to leverage results from a study that Actavis did which looked at the effects of alcohol on Kadian [pharmacokinetics].”¹⁰⁸² Ms. Leitch “attached a copy of [*Effect of Concomitant Ingestion of Alcohol on the In Vivo Pharmacokinetics of KADIAN (Morphine Sulfate Extended Release) Capsules*] along with a StatGram that Actavis sent out summarizing the results of the study.”¹⁰⁸³ She noted that “Kadian is the only product in the category that has done such a study and which can make the ‘no dose dumping in the presence of alcohol’ claim – we think this is a significant differentiator and would like to incorporate this message into the overall Kadian safety message.”¹⁰⁸⁴

¹⁰⁷⁸ ALLERGAN_MDL_00438794 at 1.

¹⁰⁷⁹ *Id.*

¹⁰⁸⁰ *Id.*

¹⁰⁸¹ *Id.* at 2-10.

¹⁰⁸² ALLERGAN_MDL_01741504 at 1.

¹⁰⁸³ *Id.*

¹⁰⁸⁴ *Id.*

529. Actavis opted to use the open-label alcohol study as part of its marketing to prescribers, because it would be a “significant differentiator” for Kadian to be able to be the only long-acting opioid that could make a “no dose dumping in the presence of alcohol claim.”¹⁰⁸⁵ Moreover, Actavis’s salespeople “use[d] the results to talk about Kadian to prescribers.”¹⁰⁸⁶

530. In her deposition testimony, Ms. Leitch confirmed that Actavis stopped using the alcohol study and StatGram after it received the DDMAC letter in February 2010.¹⁰⁸⁷

531. More than one year after Actavis stopped using the alcohol study and StatGram, market research conducted by Genesis on behalf of Actavis found that prescribers still perceived “lack of potency loss” as a strength for Kadian for “suspected alcohol abusers” and even those with “remote issues of alcohol abuse.”¹⁰⁸⁸

532. As revealed by the Genesis market research, prescribers continued to believe Actavis’s dose dumping claims and that Kadian was safe to use with alcohol.¹⁰⁸⁹

533. In my opinion, Actavis falsely promoted Kadian as having no alcohol-induced dose-dumping effect, and failed to take reasonable measures to correct prescriber misperceptions that persisted even after Actavis ceased using this claim in its promotion of Kadian.

¹⁰⁸⁵ See ALLERGAN_MDL_01741504; Nathalie Leitch Dep., 245:16-247:5. (January 22, 2019)

¹⁰⁸⁶ Nathalie Leitch Dep., 246:17-247:5 (January 22, 2019)

¹⁰⁸⁷ *Id.* at 247:12 -248:19 (“After we got the letter from the FDA, we narrowed everything down to stick within the label.”)

¹⁰⁸⁸ See ALLERGAN_MDL_00399112, ALLERGAN_MDL_00399113 at 8-9; Nathalie Leitch Dep. ,250:8-255:21 (January 22, 2019)

¹⁰⁸⁹ *Id.*

3. Actavis's Promotion of Opioids Minimized the Risks of Addiction and Abuse.

534. Allergan's promotion minimized the addiction potential of Kadian and opioids in general.

534.1. For instance, Actavis decided not to submit the sales training manual to FDA after receipt of the DDMAC letter. Instead, it added a stamp on each page of the July 1, 2010 manual that read: "For Internal and Training Purposes Only: Not to be Distributed."¹⁰⁹⁰

534.2. Further, Actavis indicated in a Kadian Stocking Offer that:

"Concerns about abuse, addiction, and diversion, should not, however, prevent the proper management of pain."¹⁰⁹¹

534.3. Actavis also trained its salespeople with the same message in a take-home study aid.¹⁰⁹²

535. According to Actavis's marketing director Jennifer Altier, the *Kadian Learning System* was "what a [sales] rep would have received upon joining the company, to learn about Kadian and the pain environment."¹⁰⁹³ Among other things, the *Kadian Learning System* discussed "pseudoaddiction."

536. Kadian sales representatives were trained that Kadian users who were "pseudoaddicted" could be differentiated from individuals with "physical dependence,"

¹⁰⁹⁰ Acquired_Actavis_00365380; Jenniifer Altier Dep., Ex. 2 (August 2, 2018).

¹⁰⁹¹ Acquired_Actavis_00369188.

¹⁰⁹² ALLERGAN_MDL_01610522 at 109. ("Concern[s] about abuse, addiction, and diversion should not prevent the proper management of pain.")

¹⁰⁹³ Jenniifer Altier Dep., 103:10-13 (August 2, 2018).

“tolerance,” and “addiction”¹⁰⁹⁴ based upon their treatment for pain. For example, take-home study aids provided to Kadian sales representatives stated:

“The problem is even more complex because some patients who are undertreated for their physical pain show the symptoms of “pseudoaddiction.” Pseudoaddiction is a set of behaviors (Table 1-3) that are exhibited by patients with inadequately treated pain, including patients with cancer pain. Pseudoaddictive behaviors are not signs of substance abuse, but rather should be considered symptoms of inadequate treatment.”¹⁰⁹⁵

537. In my opinion, Actavis’s promotion of opioids minimized the risks of addiction and abuse.

X. MALLINCKRODT

A. Overview

538. Since 1993¹⁰⁹⁶, Mallinckrodt¹⁰⁹⁷ has sold and promoted various generic and branded opioid products. Mallinckrodt’s branded opioid products included Exalgo and Xartemis XR, and its generic products included oxycodone hydrochloride ER tablets (generic OxyContin), morphine sulfate ER tablets (generic MS Contin), generic fentanyl, generic fentanyl citrate.

539. In addition, Mallinckrodt sold and promoted various opioid addiction treatment products, such as methadone, and acknowledged the significant risk of misuse, abuse, addiction, and overdose associated with opioids.¹⁰⁹⁸

¹⁰⁹⁴ Acquired_Actavis_00188875 at 7.

¹⁰⁹⁵ ALLERGAN_MDL_00439499 at 34.

¹⁰⁹⁶ See Schedule 8.

¹⁰⁹⁷ Maillinckrodt Inc. was a subsidiary of Covidien PLC until June 28, 2013, and for purposes of this report, references to Mallinckrodt incorporate Covidien as well.

¹⁰⁹⁸ MNK-T1_0001279950 at 8. Indeed, as Mallinckrodt’s sales of its opioid products increased, Mallinckrodt recognized a growth opportunity for its addiction treatment products because of the “large and growing problem” of opioid abuse. See MNK-T1_1332076 at 4; MNK-T1_0001179053; MNK-T1_0001179054; MNK-T1_0001179057; MNK-T1_0001961222.

540. Nonetheless, Mallinckrodt utilized marketing tactics that understated risks, overstated benefits, and for indications that lacked substantial evidence to support their safety and efficacy.

B. Exalgo

541. Exalgo is an extended-release hydromorphone oral tablet. Hydromorphone is a “semi-synthetic, hydrogenated ketone of morphine which acts on the u-opioid receptors.”¹⁰⁹⁹

542. Mallinckrodt acquired the rights to distribute Exalgo from Neuromed in June 2009,¹¹⁰⁰ and received FDA approval to market Exalgo ER 8, 12, 16-mg tablets for “the management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock analgesia for an extended period of time” on March 1, 2010.¹¹⁰¹ A higher, 32-mg dose of Exalgo was approved in 2012.

543. From 2010 to 2017, Mallinckrodt’s sales of Exalgo exceeded \$717 million dollars.¹¹⁰²

1. Mallinckrodt’s Marketing Strategy for Exalgo

544. With Exalgo, Mallinckrodt’s marketing strategy for Exalgo identified an opportunity to market an extended release hydromorphone tablet to compete with OxyContin and Opana ER.¹¹⁰³ As noted in the 2011 Exalgo Marketing Plan:

The extended-release opioid market as defined above generated sales of \$6.6 billion in 2009. Sales volume is increasing by 9.5%. Within this market,

¹⁰⁹⁹ MNK-T1_0001561047 at 11.

¹¹⁰⁰ See Press Release, “Covidien Announces License Rights Acquisition Agreement,” Medtronic plc (June 17, 2009), available <http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=2003878>.

¹¹⁰¹ Exalgo Approval Letter, March 2010, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021217s000ltr.pdf (last visited March 24, 2019).

¹¹⁰² See Exhibit 5 to Mallinckrodt’s Supplemental Responses and Objections to Interrogatories Nos. 1, 5, 7, 8, 9, 16, 21, 22, 23, 27, 30, 31, 32, 33, and 35, dated January 30, 2019.

¹¹⁰³ MNK-T1_0000708777

OxyContin is the clear market leader with sales of \$3.0 billion in 2009 and 46% market share.... As expected, the branded products, because of their higher price, account for about 62% of market sales. This share will increase in 2010 as generic oxycodone ER products are no longer available.¹¹⁰⁴

545. In introducing Exalgo, Mallinckrodt also noted the minimal competition it would face from generic competition, stating “[i]t is easy to see strategically why we have chosen this market”:

The largest dollar volume is consistent with the prescription volume although certainly as a consequence of minimal generic intrusion, OxyContin represents the largest dollar volume. It is important to point out that despite Opana ER's 3% volume it translates into nearly \$300 MM. It is easy to see strategically why we have chosen this market.¹¹⁰⁵

546. A key Mallinckrodt strategy in entering the extended-release market, according to a 2010 marketing presentation, included targeting “high volume prescribers.”¹¹⁰⁶

2. Mallinckrodt Promoted Exalgo in a Manner that Understated its Risks and Overstated its Benefits

(a) Mallinckrodt Falsely Promoted Exalgo as Safer than other Opioid Products

547. As noted above, Exalgo is extended-release hydromorphone, and hydromorphone is known to have a high abuse potential and an abuse liability similar to other opioids.

547.1. The FDA Medical Reviewer in its review of Exalgo stated that “[f]rom the perspective of risk, the safety data submitted were generally consistent with those of the opioid class of drugs,” and “[t]he risks (including overdose, misuse and abuse) associated with this potent extended-release opioid appear similar to other opioids in this class.”¹¹⁰⁷

¹¹⁰⁴ MNK-T1_0001191100 at 15.

¹¹⁰⁵ MNK-T1_0000255243 at 16.

¹¹⁰⁶ MNK-T1_0000255243 at 33-34.

¹¹⁰⁷ MNK-T1_0001561047 at 8.

547.2. FDA additionally noted in its Medical Review of Exalgo that

“[h]ydromorphone has a high abuse potential at least comparably or slightly higher than oxycodone”; “[t]he PK/PD profile of altered Exalgo (8mg dosage) is similar to that of hydromorphone immediate release (8mg dosage);” “Exalgo has a high abuse potential ...,” and “Exalgo would be predicted to have high levels of abuse and diversion.”¹¹⁰⁸

548. In developing the marketing strategy for Exalgo, Mallinckrodt identified abuse and addiction as major concerns among healthcare providers and patients.

548.1. Pre-market research revealed healthcare providers were concerned about the abuse potential of opioids in addition to efficacy and availability. With respect to patients, the research found that while chronic pain had a profound impact on daily life, patients were concerned about addiction and resentful about having to take the opioids.¹¹⁰⁹

548.2. In an Exalgo Brand Strategy presentation dated April 27, 2010, Mallinckrodt acknowledged the “[n]egative perceptions of hydromorphone: old, too potent, and street value (abuse),” as a barrier to the launch of Exalgo, and planned to “Reposition Hydromorphone” by, among other things, “[d]riv[ing] understanding of the clinical data, differentiating EXALGO in the process.”¹¹¹⁰

549. As with Purdue, Mallinckrodt claimed that Exalgo was superior to other opioid products because of the elimination of the “peaks and troughs.”

¹¹⁰⁸ MNK-T1_0001561047 at 8.

¹¹⁰⁹ MNK-T1_0000861442; *see also* MNK-T1_0000861227 at 1 (doctor is “[e]xtremely concerned about safety and abuse since pill can be crushed, chewed. They are wondering why we didn’t use new technology to prevent this.”).

¹¹¹⁰ MNK-T1_0000255243 at 476.

549.1. For example, in the Mallinckrodt presentation from April 27, 2010, discussed above, Mallinckrodt described how it could reposition Exalgo as a “safe and effective” product:

EXALGO Brand Strategy

Establish EXALGO as a leading safe and effective treatment for chronic pain through **repositioning hydromorphone** with the consistent and steady pharmacokinetic profile of EXALGO, **driving successful** prescriber and patient experience with **safe and appropriate** use and the development of **product advocacy** through thought leader support.¹¹¹¹

549.2. In this same presentation, Mallinckrodt described an Exalgo sales aid that “[c]ompare[s] the steady-state plasma concentrations of EXALGO to those IR formulations,” noting that “[e]specially compelling is the reduction of peaks and troughs.”¹¹¹²

549.3. In a 2011 Marketing Plan, Mallinckrodt’s positioning statement for Exalgo focused on the benefits from its pharmacokinetic profile:, stating that Exalgo “eliminates the peaks and troughs” and provides “smooth, steady hydromorphone blood levels” “resulting in once-daily predictable chronic pain relief.”¹¹¹³

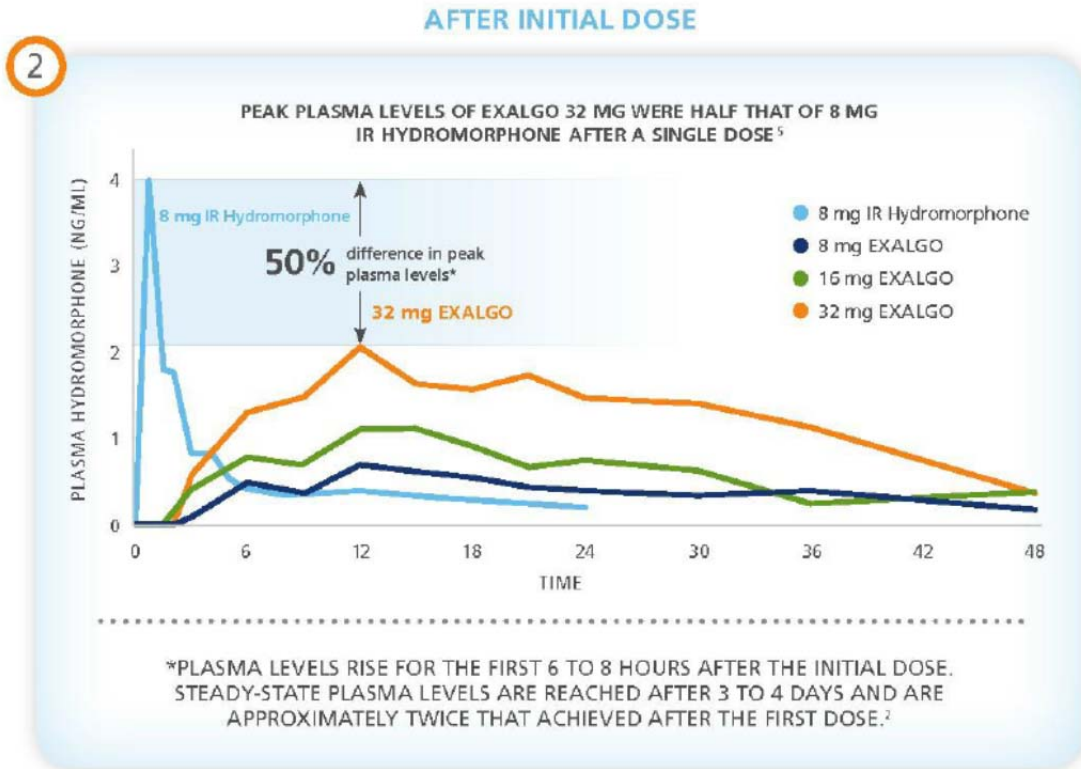
549.4. For example, in a “Master Sales Aid Implementation Guide,” Exalgo sales representatives were told to use the graph below “to show there was a 50% difference in peak concentration after the initial dose” as compared to hydromorphone.¹¹¹⁴

¹¹¹¹ MNK-T1_0000255243 at 48 (original emphasis).

¹¹¹² MNK-T1_0000255243 at 66.

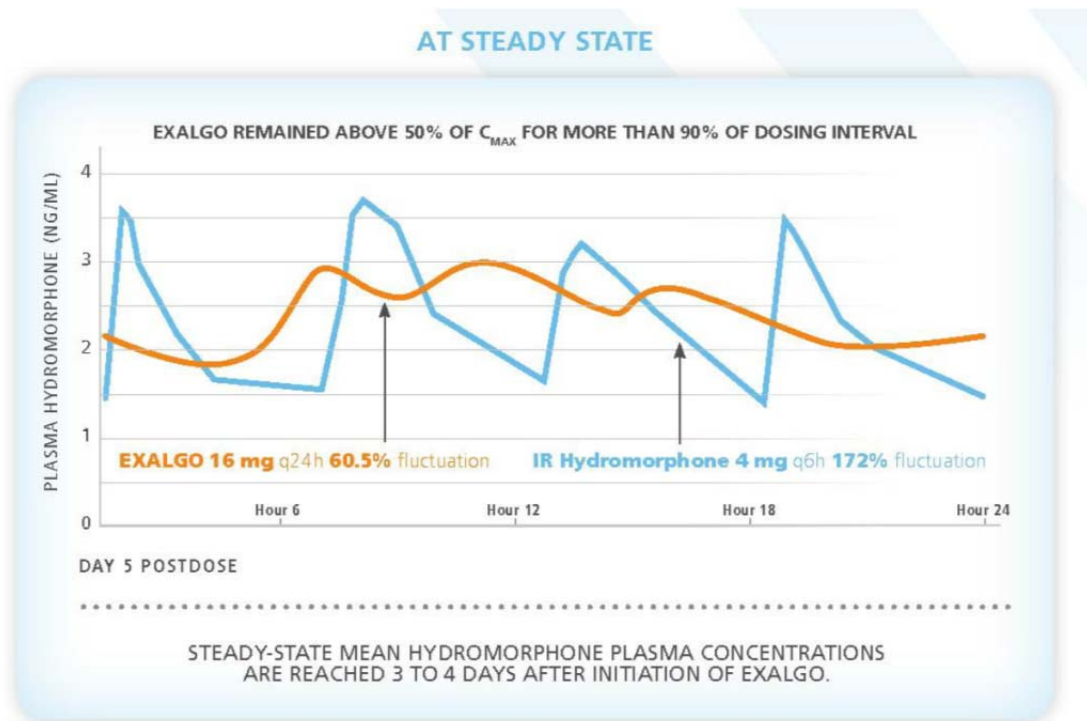
¹¹¹³ MNK-T1_0001191100 at 28.

¹¹¹⁴ MNK-T1_0000742073 at 5.



549.5. The guide also included the following with the instruction “with this graph, your physician will see the sharp contrast between the plasma concentrations of IR hydromorphone (blue line) and Exalgo at steady state (orange line). The IR hydromorphone was dosed 4 times a day and had 172% fluctuation, whereas once-daily Exalgo had only a 60.5% fluctuation.”¹¹¹⁵

¹¹¹⁵ MNK-T1_0000742073 at 5. This graph is included in the 2016 version of the Exalgo label.



549.6. In addition to comparing Exalgo to hydromorphone, Mallinckrodt's Master Sales Aid and Implementation Guide for Exalgo also instructed its sales force to state "our data indicate that Exalgo patients receive a much lower daily morphine equivalent dose than Opana ER and OxyContin patients – 78% lower than Opana ER and 92% lower than OxyContin," which falsely suggested that Exalgo was safer and more efficacious than Opana ER and OxyContin.¹¹¹⁶

549.7. A script for a Mallinckrodt paid speaker also made reference to Exalgo's peak and troughs, comparing them to immediate-release hydromorphone and again noting "[l]ess fluctuations appear in the plasma":

Slide number 6 reviews some of the ways we might attempt to treat pain using medications. On the right hand side of the slide, there are three types of medications portrayed. The first is if somebody is using a typical short-acting opioid given on a q. 6 hour dosing and the classic peak and trough presentation is seen. Even in a steady state situation, there will be

¹¹¹⁶ MNK-T1_0000742073 at 7.

significant fluctuations in peak and trough during the course of the day if someone is only using an immediate release drug.

The second graph shows the plasma concentrations of an individual on a q. 12 hour dosing drug. And you'll notice that there are still peaks and troughs, though less than what are seen in the q.i.d. delivered drug. The final graph at the bottom is someone taking a q. 24 hour drug. Less fluctuations appear in the plasma.¹¹¹⁷

550. In my opinion, Mallinckrodt falsely promoted Exalgo as safer than other opioid products.

(b) Mallinckrodt's sales training misleadingly minimized the risks associated with higher doses of opioids and encouraged sales representatives to make misleading claims regarding abuse deterrence

551. After receiving FDA approval for a higher, 32 mg dose of Exalgo, Mallinckrodt's sales of this dose failed to meet expectations, with a Regional Sales Manager for Exalgo stating on March 27, 2013, "[w]e have to shift as much business, when clinically needed, to 32mg as soon as possible to protect the brand," which faced generic competition for its lower doses.¹¹¹⁸

552. Mallinckrodt told its sales force that the dose of Exalgo could be adjusted upward without identifying the potentially fatal risks of respiratory depression and the increased risk of abuse. For example, in a May 11, 2012 email to Mallinckrodt's sales force, Mallinckrodt provided a sales training song by "Propah Dose by the Might Converters" to "[g]et INSPIRED" to sell Exalgo.¹¹¹⁹ In introducing the song, two actors—"Mike" and "Melissa"—stated: "We hope you have embraced the new INSPIRE messaging and are gaining your customer's attention by being bold and setting EXALGO apart as an innovative delivery system for treating chronic pain." The song told sales representatives to "[m]ake sure you don't stop" increasing the dose of

¹¹¹⁷ MNK-T1_0000100452 at 4.

¹¹¹⁸ MNK-T1_0000124624 at 1.

¹¹¹⁹ MNK-T1_0004610227 at 1.

Exalgo “[c]ause your patient needs relief, mon” but did not identify the risks of increasing the dose of Exalgo:

You can start at the middle
You can start at the top
You can start with very little
But that’s not where you should stop
Cause your patient needs relief, mon
...
So when you start at the middle
Or you start at the top
Or you start with a little
Make sure you don’t stop
Cause your patient needs relief, mon¹¹²⁰

553. Mallinckrodt also told its sale force to highlight Exalgo’s physio-chemical properties to physicians despite Exalgo’s lack of FDA approval as an abuse-deterrent opioid product. For instance, an April 18, 2013 update stated:

Do not proactively discuss this announcement with your customers . . . If your customers ask if EXALGO is abuse deterrent: Ensure the physician understands that EXALGO cannot claim abuse/tamper resistance, but there are physical properties to the tablet of which they should be aware. “Doctor, while we can make no claims concerning abuse potential, you may be interested to know that there are several interesting physical properties of EXALGO. It has a hard outer shell that is difficult to crush. If a tablet is crushed it forms large particles. Also, it agglomerates when exposed to water when crushed. Of course, it is important to keep EXALGO out of the hands of inappropriate patients. However, let’s discuss an appropriate patient for EXALGO like the Elaine patient. This is a patient you likely see multiple times a day who may benefit from the true 24-hour dosing EXALGO provides.”¹¹²¹

554. In my opinion, Mallinckrodt’s sales training misleadingly minimized the risks associated with higher doses of opioids and encouraged sales representatives to make misleading claims regarding abuse deterrence.

¹¹²⁰ MNK-T10004166098 at 1-2.

¹¹²¹ MNK-T1_0000122999 at 1-2.

**(c) Mallinckrodt Misleadingly Minimized the Risk of Addiction
and Funded the CARES Alliance, Which Likewise
Understated the Risk of Addiction**

555. Mallinckrodt understated the risk of addiction through unbranded promotion and the CARES Alliance.

555.1. According to a May 14, 2014 email, Mallinckrodt maintained unbranded Pain Management pocketcard sets for distribution at trade shows.¹¹²² Under the heading “[g]eneral [a]pproach to [p]ain [m]anagement,” the pocketcards told healthcare providers “[a]ddiction rarely occurs unless there is a hx of abuse.”¹¹²³

555.2. Similarly, *Defeat Chronic Pain Now!*,¹¹²⁴ sponsored by Mallinckrodt and positioned as an important source of information for patients¹¹²⁵ understated the risk of addiction, stating “[w]hen chronic pain patients take opioids to treat their pain, they rarely develop a true addiction and drug craving;” “[t]he bottom line: Only rarely does opioid medication cause a true addiction when prescribed appropriately to a chronic pain patient who does not have a prior history of addiction;” and “[h]ere are the facts. It is very uncommon for a person with chronic pain to become ‘addicted’ to narcotics IF (1) he doesn’t have a prior history of any addiction and (2) he only takes the medication to treat pain.”¹¹²⁶

¹¹²² MNK-T1_0002159712.

¹¹²³ MNK-T1_0001531484 at 1.

¹¹²⁴ GALER, BRADLEY & C. ARGOFF., *DEFEAT CHRONIC PAIN NOW!* (2010).

¹¹²⁵ The CARES Alliance catalogue listed *Defeat Chronic Pain Now!* as a “Patient Tool.” MNK-T1_0001493093 at 13; *see also* (MNK-T1_0000098099) (“Example of Education and Enabling Tools” “Patient” “Defeat Chronic Pain Now”)

¹¹²⁶ GALER, BRADLEY & C. ARGOFF., *DEFEAT CHRONIC PAIN NOW!* (2010) at 176-178.

556. In my opinion, Mallinckrodt misleadingly minimized the risk of addiction and funded the CARES Alliance which likewise understated the risk of addiction.

(d) Mallinckrodt Misleadingly Told Health Care Providers that Patients Exhibiting Signs of Addiction Were Likely “Pseudoaddicted” and in Need of Additional Opioids to Treat Pain

557. As discussed above, pseudoaddiction is not supported by substantial evidence.

558. Notwithstanding the lack of substantial evidence to support the concept of pseudoaddiction, Mallinckrodt promoted pseudoaddiction through the CARES Alliance, in unbranded pocket cards distributed at trade shows, and in sales training materials.

559. The CARES Alliance supported by Mallinckrodt disseminated “education” and literature that recognized pseudoaddiction as a medical condition despite a lack of substantial evidence.

559.1. A June 2010 CARES Alliance Opioid Clinical Management Education Module in a slide entitled “Pseudoaddiction” taught healthcare providers “Aberrant behaviors due to undertreatment of pain” “includ[e] inappropriate drug seeking behaviors. Unlike true addiction, when pain is effectively treated [a]berrant behaviors resolve.”¹¹²⁷

559.2. The speaker’s notes in the same Education Module stated “Pseudoaddiction: Patients who are receiving an inadequate dose of opioid medications and seek more.”¹¹²⁸

¹¹²⁷ MNK-T1_0001492929 at slide 21.

¹¹²⁸ *Id.* at slide 49.

559.3. The Glossary of Terms in the Education Module similarly defined pseudoaddiction as “Patients who are receiving an inadequate dose of opioid medication and seek more pain medication to obtain relief.”¹¹²⁹

559.4. The speaker’s notes for a slide entitled “Managing Nonadherent Patients” in an April 13, 2011 CARES Alliance Education Module sponsored by Mallinckrodt similarly stated “Pseudoaddiction: Patients who are receiving an inadequate dose of opioid medications and seek more.”¹¹³⁰

559.5. The Glossary of Terms in the Education Module similarly defined pseudoaddiction as “Patients who are receiving an inadequate dose of opioid medication and seek more pain medication to obtain relief.”¹¹³¹

559.6. A CARES Alliance brochure entitled “Opioid Clinical Management Guide: A Resource for Responsible Opioid Prescribing and Use” instructed “[s]ome patients may exhibit aberrant behaviors, including inappropriate drug seeking behaviors when pain is undertreated. Unlike true addiction, however, these behaviors resolve and function and quality of life increase when pain is effectively treated.”¹¹³²

559.7. The CARES Alliance also promoted *Responsible Opioid Prescribing: A Physician’s Guide* by Scott Fishman, M.D.¹¹³³ *Responsible Opioid Prescribing* taught healthcare providers to “[b]e aware of the distinction between *pseudoaddiction* and

¹¹²⁹ *Id.* at slide 63. An August 10, 2010 “Train-the-Trainer” Exalgo REMS & CARES Alliance Education Module for Steven Passik, PhD, similarly instructed that “[p]seudoaddiction” was an “[a]berrant behavior[] due to undertreatment of pain” and that “unlike true addiction, when pain is effectively treated [a]berrant behaviors resolve” and defined pseudoaddiction as “[p]atients who are receiving an inadequate dose of opioid medication and seek more pain medication to obtain pain relief.” MNK-T1_0001490570 at slides 23, 65.

¹¹³⁰ MNK-T1_0001492936 at slide20.

¹¹³¹ *Id.* at slide73.

¹¹³² MNK-T1_0007097450 at 5.

¹¹³³ Kevin Webb Dep. Tr. Ex. 15 at 7 (MNK-T1_0001493093 at4).

addiction. Patients who are receiving an inadequate dose of opioid medication often ‘seek’ more pain medications to obtain pain relief. This is called pseudoaddiction because healthcare practitioners can mistake it for the drug-seeking behavior of addiction . . .

Some common signs of pseudoaddiction resulting from inadequate analgesia are:

Requesting analgesics by name, Demanding or manipulative behavior, Clock watching, Taking opioid drugs for an extended period, Obtaining opioid drugs from more than one physician [] and Hoarding opioids.”¹¹³⁴

560. In addition, Mallinckrodt distributed the American Society of Pain Educators Pocket Guides at trade shows¹¹³⁵ and paid to have Exalgo in the drug table of the Guides.¹¹³⁶ The pocket cards told healthcare providers that “drug- seeking behavior focused on pain relief, due to undertreatment of pain” was “[b]ehavior [that] normalizes with adequate analgesia.”¹¹³⁷

561. Mallinckrodt likewise trained its sales force on the concept. “Module 7” on “Misuse, Abuse, Diversion and Addiction” stated “[t]his module begins with definitions of the common terminology associated with opioid use . . . Patients with pain who are prescribed opioid therapy may exhibit a range of behavioral responses” including “pseudoaddiction” defined as “result[ing] from inadequate analgesia (not addiction), yet patient display symptoms that can mimic addiction.”¹¹³⁸

¹¹³⁴ MNK-T1_0001072077 at page 62 of *Responsible of Opioid Prescribing: A Physician’s Guide*. The book added that “these same behavioral signs can indicate addiction. One way to discriminate between the two is to observe as closely as possible the functional consequences of opioid use. Whereas pseudoaddiction resolves when the patient obtains adequate analgesia, addictive behavior does not. Consultation with an addiction medicine specialist or psychiatrist may be necessary at the point when addiction becomes a concern.”

¹¹³⁵ MNK-T1_0002159712.

¹¹³⁶ MNK-T1_0001786857.

¹¹³⁷ MNK-T1_0001786865 at 9.

¹¹³⁸ MNK-T1_0007169529 at 23.

562. In my opinion, Mallinckrodt misleadingly told healthcare providers and trained its sales force that patients exhibiting signs of addiction were likely “pseudoaddicted” and in need of additional opioids to treat pain.

C. Xartemis XR

563. Xartemis XR is an extended-release combination of oxycodone and acetaminophen.

564. Mallinckrodt received FDA approval for Xartemis XR Extended Release Tablets 7.5/325 mg for “the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate” on March 11, 2014.¹¹³⁹

565. From 2014 to 2017, Mallinckrodt’s sales of Xartemis XR exceeded \$13.1 million dollars.¹¹⁴⁰

1. Mallinckrodt’s Marketing Strategy for Xartemis

566. According to the preapproval Launch “Playbook” for Xartemis, Mallinckrodt’s “[p]ositioning statement” for Xartemis XR was “Superior Percocet”¹¹⁴¹ as the first long acting oxycodone/acetaminophen product for acute pain patients. The Playbook elaborated that the positioning statement would be directed to “[health care providers] who routinely prescribe Percocet.” This positioning statement would be communicated to health care providers with the message that Xartemis XR “is the first and only controlled-release oxycodone/APAP product” that “provides fast-acting and long-last pain relief without concerns about abuse” because “it’s formulated with unique physical properties that yield an improved pharmacokinetic profile.”¹¹⁴²

¹¹³⁹ MNK-T1_0002446841 at 1, MNK-T1_0001957485.

¹¹⁴⁰ See Ex. 5 to Mallinckrodt’s Supplemental Responses and Objections to Interrogatories Nos. 1, 5, 7, 8, 9, 16, 21, 22, 23, 27, 30, 31, 32, 33, and 35, dated Jan. 30, 2019.

¹¹⁴¹ MNK-T1_0000257748 at 19.

¹¹⁴² MNK-T10000257748 at 19.

567. Mallinckrodt's "Playbook" for Xartemis XR stated this message was provided to prescribers so that "they can confidently provide a superior treatment that is more responsible to patients and society."¹¹⁴³

568. In preparing to launch Xartemis XR, Mallinckrodt's "[m]ission" was to "[e]stablish market appreciation and need for abuse-resistant technology for the treatment of acute pain" and "[e]stablish XARTEMIS as a new treatment, well-know drug combination with broad clinical utility," including "Abuse Resistant Technology [that] provides HCP greater comfort to prescribe due to advantages compared to IR OC/APA when tampered/abuse."¹¹⁴⁴

569. According to a draft marketing presentation titled "GO TIME" by Mallinckrodt's Product Director for Xartemis XR, Michael Wessler, "[s]uccessful commercialization of XARTEMIS XR is reliant upon challenging currently engrained prescribing habits,"¹¹⁴⁵ i.e. that the treatment of acute pain warranted a long-acting opioid product with abuse-deterrent properties.

570. Prior to the approval of Xartemis XR, Mallinckrodt utilized the CARES Alliaceto redefine Mallinckrodt as responsible company developing ADT products in an era of increasing opioid abuse.¹¹⁴⁶

571. In an October 16, 2013 presentation, an "[a]dvocacy initiative" of Mallinckrodt included "[r]ebranding/expanding CARES Alliance ... as a vehicle to amplify the collaborative efforts of Mallinckrodt and its advocacy partners to address the societal burden of the unintended

¹¹⁴³ MNK-T1_0000257748 at 19. The Xartemis XR Launch Playbook also identified "[c]ritical success factors" for the launch of Xartemis including "[g]et the physicians to rethink 15mg of Oxy in one dose," "[e]levate the unmet need(s) in the acute pain space," "[m]aximize touch points with high-potential targets through appropriate promotional mix" and "[e]mploy tactics to achieve greatest ROI." *Id.* at 7.

¹¹⁴⁴ MNK-T1_0000230267 at 2.

¹¹⁴⁵ MNK-T1_0000143151 at 5.

¹¹⁴⁶ See MNK-T1_0000225603 at 1.

consequences of prescription opioid abuse, misuse, and diversion.”¹¹⁴⁷ In addition, another initiative included in this presentation included “[l]everage C.A.R.E.S. to proactively define Mallinckrodt’s corporate reputation ... to bring market awareness to Mallinckrodt’s efforts as a responsible company in the area of opioid management.”¹¹⁴⁸

2. Mallinckrodt Misleadingly Marketed Xartemis as Having a Lower Potential for Abuse as Compared to Other Opioid Products.

572. In its NDA submission for Xartemis XR, Mallinckrodt maintained that Xartemis XR had abuse deterred properties,¹¹⁴⁹ and sought labeling that identified Xartemis XR as having abuse deterrent properties.

573. In 2013, FDA determined that Mallinckrodt lacked sufficient clinical data to support the abuse deterrent properties of Xartemis XR.

573.1. In the Risk Assessment and Risk Mitigation Review of Xartemis XR dated October 17, 2013, FDA noted that “[t]he only product characteristic difference between the immediate-release product and Xartemis XR is duration of action.”¹¹⁵⁰

573.2. A few months later on November 7, 2013, the Cross Discipline Team Leader issued her memorandum, stating that ADT labeling would not be permitted:

A CDTL memo was filed in FARRTS on November 7, 2013, that reviewed the submission for Xartemis CR including summary of the Controlled Substance Staff (CSS) review of the in vivo and in vitro data submitted in the original NDA submission by the Applicant to support abuse deterrent (AD) properties of Xartemis CR and labeling language regarding these properties. The conclusion reached at that time was that the Applicant had adequately demonstrated safety and efficacy of Xartemis XR for the treatment of acute pain, however the in vitro and in

¹¹⁴⁷ MNK-T1_0000222031 at 6.

¹¹⁴⁸ MNK-T1_0000222031 at 6.

¹¹⁴⁹ MNK-T1_0000000313 at 1.

¹¹⁵⁰ FDA Risk Assessment and Risk Mitigation Review at 3, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204031Orig1s000RiskR.pdf

vivo data submitted with the NDA were not sufficient to support the abuse deterrent properties or labeling for Xartemis XR, as determined by CSS.¹¹⁵¹

574. Despite not receiving FDA approval to market Xartemis XR as having abuse deterrent properties, Mallinckrodt promoted Xartemis XR as having reduce abuse potential as compared to other opioids.

574.1. For example, in a Mallinckrodt media training document, Mallinckrodt acknowledged that FDA had denied its request for abuse deterrent labeling for Xartemis ER but nonetheless promoted various aspects of its abuse-deterrent technology, stating:

Q2. Can XARTEMIS XR be easily crushed?

A2. XARTEMIS XR can be crushed, but becomes a difficult-to-manage powder when it interacts with any liquids. Due to these product properties, in in vitro studies crushed XARTEMIS XR became a stiff, unmanageable gel when mixed with small amounts of water.

If asked about Zohydro:

Zohydro is formulated as a capsule. Since we do not have access to their formulation data, we cannot comment on this.

Q3. Does XARTEMIS XR have abuse-deterrence data that the FDA did not recognize?

A3. While the approved label for XARTEMIS XR does not include abuse-deterrent language, Mallinckrodt conducted extensive lab testing and a Human Abuse Liability (HAL) study with XARTEMIS XR. Data from this study were presented in scientific presentations at PAINWeek, September 4-7, 2013. Mallinckrodt will continue working closely with the FDA to develop more data to characterize abuse-deterrence features of XARTEMIS XR and other products utilizing this technology platform. Mallinckrodt is conducting additional studies and plans to provide additional data by the end of the year.

Should there be a FN to MNK-T1_0000102166?

1.1. In addition, Mallinckrodt sales representatives were provided with a sales aid containing a chart titled “less drug high with tampered Xartemis – study subjects reported less drug high with crushed vs. intact Xartemis.”¹¹⁵²

¹¹⁵¹ FDA Cross Discipline Team Leader Mem. at 2, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204031Orig1s000CrossR.pdf

¹¹⁵² MNK-T1_0000122250 at 4.

1.2. In this same aid, Mallinckrodt stated that “[l]ess drug high with Xartemis – study subjects reported less drug high with Xartemis vs Percocet” and “Xartemis is the only agent to meet all 3 endpoints assessing abuse potential – intact Xartemis produced subjective responses on scales of drug high, drug liking, and good drug effects that were significantly less than intact Percocet at an equivalent dose.”¹¹⁵³

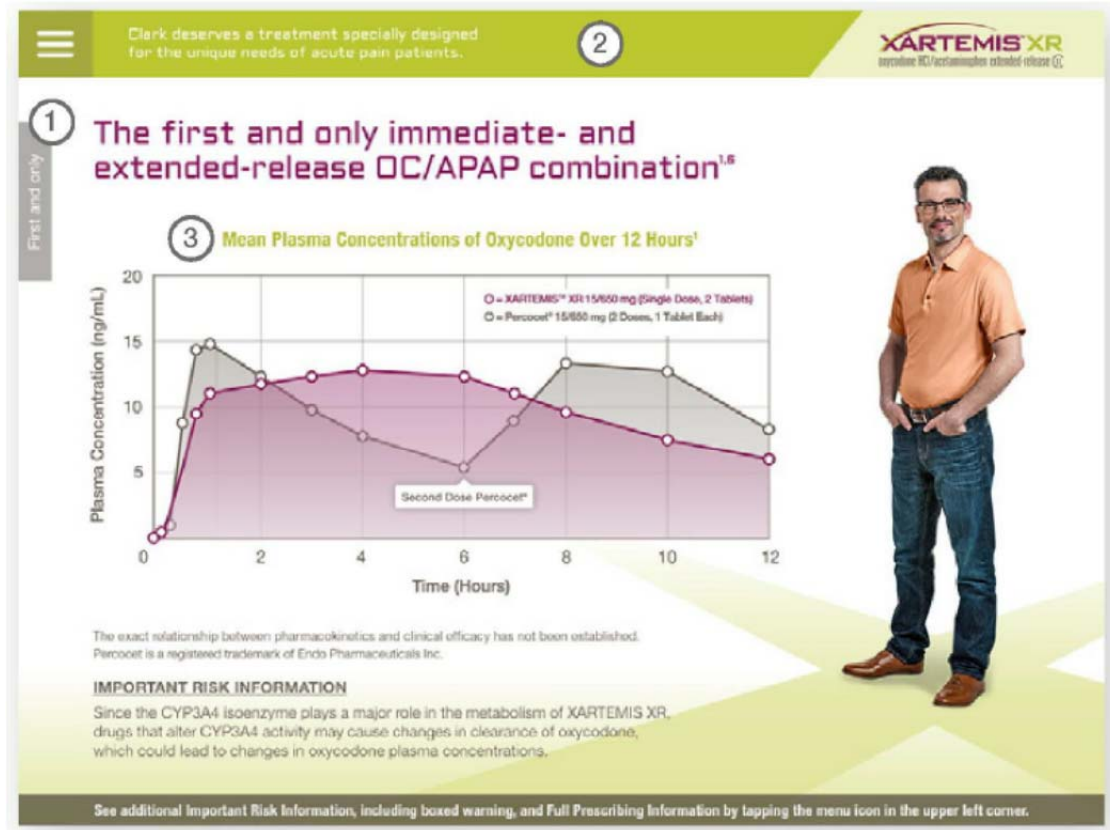
2. Just as with Exalgo, and similar to the strategy employed by Purdue in falsely marketing OxyContin as having reduced abuse potential, Mallinckrodt’s marketing highlighted the “fewer peaks and troughs” of Xartemis ER as compared to other opioid products.

2.1. For example, in the following promotional chart shown healthcare providers, Mallinckrodt instructed its sales representatives “[t]o detail this screen, you might say... The graph shows Xartemis XR maintaining plasma concentrations with fewer peaks and troughs than Percocet over 12 hours. It also demonstrates a more prolonged release versus Percocet.”

¹¹⁵³ MNK-T1_0000122250 at 5, 7. The aid likewise claimed that Xartemis was “formulated” to be “less attractive for abuse”—a claim FDA specifically rejected.

Xartemis is formulated to be less attractive for abuse” and “when ground with mortar and pestle, the percentage of release of oxycodone over the first hour was reduced with Xartemis compared to intact tablets” and “when crushed and exposed to moisture, Xartemis forms a viscous hydrogel that resists passage through a needle.”

Id. at 9.



574.2. In another sales aid, sales representatives were told “controlled release inhibits drug high with Xartemis – after a rapid initial rise, intact Xartemis yielded a lower rate of rise of oxycodone plasma concentrations than equivalent doses of intact Percocet” and “when crushed and swallowed, Xartemis yielded lower rate of rise of oxycodone plasma concentrations than intact Xartemis and intact or crushed Percocet.”¹¹⁵⁴

575. In marketing Xartemis XR, Mallinckrodt encouraged “aggressive” promotion by its sales force.

575.1. On May 19, 2014, several months after the launch of Xartemis, Hugh M. O’Neill, Mallinckrodt’s President of Specialty Pharmaceuticals, stated in an email to Stacy A. Chick, Mallinckrodt’s Vice President of Specialty Sales, “I would also like to take our highest performing 10% of reps and bring them together on a weekend to turn

¹¹⁵⁴ MNK-T1_0000122250 at 8.

them loose on the organization and the non-prescribing physicians . . . The bottom line is [] one common goal—GENERATE Prescriptions. Everything else that is not generating prescriptions should become a secondary priority.”¹¹⁵⁵

575.2. Mallinckrodt recognized “top performing [sales] representatives” with “incentive program[s].”¹¹⁵⁶ For example, the “Fast Start Challenge Reward Trip” rewarded “top performing representatives” with an opportunity to “have two minutes to run through a warehouse” and “grab things off the shelves in [a] warehouse that was set up by the vendor and they could have that . . . as a gift to themselves.” The items included “[e]lectronic items, games, toys, a myriad of things.”¹¹⁵⁷

575.3. An August 15, 2013 email from Krishnan Paranjothi, Mallinckrodt Senior District Sales Manager, Kansas City, District to Jason Daharsh and other sales representatives counseled “You only have 1 responsibility, SELL BABY SELL!”¹¹⁵⁸

576. In my opinion, Mallinckrodt falsely marketed Xartemis as having a lower potential for abuse as compared to other opioid products.

XI. THE OPIOID MANUFACTURERS’ SUPPORT FOR AND INVOLVEMENT WITH PAIN ADVOCACY, PROFESSIONAL MEDICAL AND TRADE GROUP ORGANIZATIONS, EXPANDED THE USE OF OPIOIDS AND INCREASED THE RISK OF ABUSE

577. The opioid manufacturer addressed in this report, as briefly described in the above sections, provided support to pain advocacy, professional medical organizations, and trade group

¹¹⁵⁵ MNK-T1_0000545754 at 4; *see also* MNK-T1_0000545281 at 3; MNK-T1_0004158296.

¹¹⁵⁶ Ron Wickline Dep. Tr. 121:15-124:15; Mallinckrodt sales representatives were paid a “base salary” and received a “variable incentive performance-based component of their compensation.” Stacey Chick Dep. Tr. 170:19-171:22. The incentive performance-based component of their compensation was based on “number of prescriptions” and “potential in the territory.” *Id.* at 171:23-172:1, 172:4-7.

¹¹⁵⁷ *Id.* at 123:23-124:15

¹¹⁵⁸ MNK-T1_0002803531 at 1.

organizations, and were involved in varying ways in the development and dissemination of guidelines and other promotional materials published by these groups that served the common purpose of expanding the use of opioids.

578. Through these guidelines and other materials, the opioid manufacturers contributed to altering the standard of care for the treatment of pain by encouraging healthcare providers to view pain as a “fifth vital sign” that demanded aggressive treatment with opioids.

579. In addition, these guidelines and materials echoed certain statements made by the manufacturers regarding the risks and benefits of opioids that lacked substantial supporting evidence and were false and misleading.

580. As discussed below, the opioid manufacturers’ support for and involvement with pain advocacy, professional medical and trade group organizations, expanded the use of opioids and increased the risk of addiction abuse, overdose and death.

A. American Pain Society

581. According to its bylaws, the American Pain Society (“APS”) is a “multidisciplinary community that brings together a diverse group of professionals to increase the knowledge of pain and transform public policy and clinical practice.”¹¹⁵⁹

582. Since at least 1995, APS has received funding from several opioid manufacturers.

582.1. Between 1997 and 2012, Purdue paid the APS more than \$3,000,000.00.¹¹⁶⁰

582.2. Between 1997 and 2012, Janssen paid the APS more than \$1,700,000.00.¹¹⁶¹

¹¹⁵⁹ See <http://americanpainsociety.org/uploads/about/APS%20Bylaws%20revised%2001.21.2019.pdf>; JAN-MS-00409411.

¹¹⁶⁰ SFC00000001.

582.3. Between 1998 and 2012, Endo paid the APS \$4,468,253.10.¹¹⁶²

582.4. Between 2009 and 2013, the APS was paid \$278,000.00 by Covidien and \$218,000.00 by Teva.¹¹⁶³

583. APS has maintained a “Corporate Council” program that is sponsored by opioid manufacturers. Through this program, APS “connects” members of this “Corporate Council” to “multidisciplinary leaders in the science of pain.” Members of APS’s Corporate Council include Endo, Actavis, Mallinckrodt, Purdue, and Janssen.¹¹⁶⁴

584. In addition, APS has maintained an “APS Clinical Guidelines Program” funded by opioid manufacturers. In exchange for sponsorship, opioid manufacturers are permitted “to sit on the founding members’ guideline committee and provide input into topics for guideline development, as well as suggestions of clinicians for participation in the guidelines development process, methods of dissemination/adoption, etc.”¹¹⁶⁵ Members of APS’s Guidelines Program include Purdue, Endo, and Janssen.¹¹⁶⁶

585. As described below, APS has published newsbulletins and guidelines that were authored by individuals with direct ties to opioid manufacturers and which contained the same misleading statements regarding the benefits and risks of opioids as those used by opioid manufacturers in their branded promotion.

¹¹⁶¹ JJ-SFC-00000001.

¹¹⁶² ENDO-OR-CID-00754369 at 30.

¹¹⁶³ APS-MDL00000001.

¹¹⁶⁴ TEVA_MDL_A_00499668 at 24; *see also* U.S. Senate Homeland Security & Governmental Affairs Committee, Minority Staff Report (2018), *Fueling an Epidemic (Report Two) – Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups* at 13.

¹¹⁶⁵ ENDO-OPIOID_MDL-06234663.

¹¹⁶⁶ PKY181215749 at 14; PKY181775488.

1. APS/AAPM Guideline – The Use of Opioids for the Treatment of Chronic Pain

586. In 1997, in a joint publication with the American Academy of Pain Medicine (“AAPM”), APS and AAPM published a guideline titled “The Use of Opioids for the Treatment of Chronic Pain,”¹¹⁶⁷ containing the following misleading statements regarding opioids:

586.1. “Studies indicate that the de novo development of addiction when opioids are used for the relief of pain is low.”¹¹⁶⁸

586.2. “[E]xperience has shown that known addicts can benefit from the carefully supervised, judicious use of opioids for the treatment of pain due to cancer, surgery, or recurrent painful illnesses[.]”¹¹⁶⁹

586.3. “It is now accepted by practitioners of the specialty of pain medicine that respiratory depression induced by opioids tends to be a short-lived phenomenon, generally occurs only in the opioid-naive patient, and is antagonized by pain. Therefore, withholding the appropriate use of opioids from a patient who is experiencing pain on the basis of respiratory concerns is unwarranted.”¹¹⁷⁰

586.4. “Furthermore, for most opioids, there does not appear to be an arbitrary upper dosage limit, as was previously thought.”¹¹⁷¹

586.5. “The undertreatment of pain in today’s society is not justified. This joint consensus statement has been produced pursuant to the missions of both organizations, to

¹¹⁶⁷ PPLPC051000030818 at 2.

¹¹⁶⁸ PPLPC051000030818 at 2.

¹¹⁶⁹ PPLPC051000030818 at 2.

¹¹⁷⁰ PPLPC051000030818 at 2.

¹¹⁷¹ PPLPC051000030818 at 2.

help foster a practice environment in which opioids may be used appropriately to reduce needless suffering from pain.”¹¹⁷²

587. The authors of this guideline included those with ties to opioid manufacturers, including: J. David Haddox, M.D.,¹¹⁷³ David Joranson,¹¹⁷⁴ Richard Payne, M.D.,¹¹⁷⁵ and Richard Portenoy, M.D.¹¹⁷⁶

588. In the same year that this APS guideline was published, the following manufacturers made the following payments to APS:

588.1. For example, in 1997, Purdue reportedly paid \$48,501 and Janssen paid \$146,245 to the APS.¹¹⁷⁷

588.2. Likewise, Purdue paid \$36,800 and Janssen paid \$43,500 to the AAPM in 1997.¹¹⁷⁸

589. This guideline was used by opioid manufacturers in promoting their opioid products and opioids in general.¹¹⁷⁹

¹¹⁷² PPLPC051000030818 at 4.

¹¹⁷³ At the time, Dr. Haddox was a paid speaker for Purdue. *See, e.g.*, PKY180955294 at 1. He was subsequently employed by Purdue as the Vice President of Risk Management and Policy. J. David Haddox Depo. Tr. 57:7-18.

¹¹⁷⁴ Mr. Joranson is the former director of the University of Wisconsin Pain & Policy Study Group, which was funded by the opioid manufacturers. ENDO-OPIOID_MDL-00658641 at 2-3. The Pain and Policy Study Group also received payments from the manufacturers. *See, e.g.* ENDO-OR-CID-00754369 at 30, SFC00000001.

¹¹⁷⁵ At the time, Dr. Payne was a paid speaker for Purdue. *See, e.g.*, PKY180256893 at 1, PKY180256892 at 1, PKY180783690 at 1.

¹¹⁷⁶ At the time, Dr. Portenoy was a paid speaker for Purdue. *See, e.g.*, PKY180357269 at 1.

¹¹⁷⁷ 2012.06.08 Purdue Summary of Payments by Name and Year SFC00000001; J&J Janssen SFC 2012 Submission JAN00000001.

¹¹⁷⁸ 2012.06.08 Purdue Summary of Payments by Name and Year SFC00000001; J&J Janssen SFC 2012 Submission JAN00000001.

¹¹⁷⁹ *See, e.g.*, PKY181199494 at 17, 25; PKY181137481 at 8; ALLERGAN_MDL_02158487 at 1; ABT-MDL-KY-0009437 at 54; ENDO-OPIOID_MDL-05967764 at 1.

2. APS/AAPM/ASAM – Definitions Related to the Use of Opioids for the Treatment of Pain

590. In 2001, APS developed consensus “Definitions Related to the Use of Opioids for the Treatment of Pain” in coordination with AAPM and the American Society of Addiction Medicine (“ASAM”), containing the following misleading statement concerning pseudoaddiction: “An individual's behaviors that may suggest addiction sometimes are simply a reflection of unrelieved pain or other problems unrelated to addiction.”¹¹⁸⁰

591. In the same year that this 2001 APS/AAPM/ASAM guideline was published, the following manufacturers made the following payments to APS/AAPM/ASAM:

591.1. For example, in 2001, Purdue reportedly paid \$211,211, Janssen paid approximately \$159,000, and Endo paid \$132,400 to APS.¹¹⁸¹

591.2. Likewise, Purdue paid \$80,273, Janssen paid \$66,764, and Endo paid \$22,000 to AAPM in 2001.¹¹⁸²

591.3. That same year, Endo paid \$10,000 to ASAM.¹¹⁸³

592. It appears that Endo may have influenced the final product,¹¹⁸⁴ and that Purdue was heavily involved in the development of these definitions. Dr. Haddox noted, “Purdue has been at the forefront of efforts to promote the proper therapeutic use of opioid analgesics, including funding the very first meeting of the AAPM/APS/ASAM

¹¹⁸⁰ PDD1502210202 at 254.

¹¹⁸¹ See SFC00000001; END00000002; JAN00000001.

¹¹⁸² END00000002; JAN00000001.

¹¹⁸³ ENDO-OPIOID_MDL-06234588; JAN00000001.

¹¹⁸⁴ See END00211516.

leadership (when I was president of AAPM) to begin the collaboration that eventually led to the Consensus statement on definitions of pain and addiction.”¹¹⁸⁵

593. This guideline was used by opioid manufacturers in promoting their opioid products and opioids in general.¹¹⁸⁶

3. APS Arthritis Guidelines

594. In 2002, the APS issued “Guidelines for the Management of Arthritis Pain,” containing the following misleading statements:

594.1. “The prevalence of addiction among patients with pain who do not have a previously existing substance abuse disorder is low.”¹¹⁸⁷

594.2. “Weissman and Haddox (1989) noted that patients who are given doses of opioids that are inadequate to relieve their pain or whose opioid dose is discontinued abruptly or tapered too rapidly may develop characteristics that resemble addiction, which they termed iatrogenic ‘pseudoaddiction.’”¹¹⁸⁸

594.3. “Tolerance to analgesia is uncommon once pain relief has been achieved and there is no progression of disease.”¹¹⁸⁹

594.4. “Opioids should be used for patients with OA and RA when other medications and nonpharmacologic interventions produce inadequate pain relief and the patient's quality of life is affected by the pain.”¹¹⁹⁰

¹¹⁸⁵ PPLP003477086 at 24.

¹¹⁸⁶ See, e.g., END00212229; ENDO-OPIOID MDL-01997737; ENDO-OPIOID_MDL-02939611 at 68; END00212229; ABT-MDL-KY-0009437 at 54.

¹¹⁸⁷ PKY181215749 at 95.

¹¹⁸⁸ PKY181215749 at 95.

¹¹⁸⁹ PKY181215749 at 96.

¹¹⁹⁰ PKY181215749 at 97.

594.5. “Extensive experience and evidence in the management of chronic malignant pain supports the use of long-acting opioids to improve patient adherence, minimize medication level peaks and valleys, and minimize side effects. These advantages also appear to apply to the use of long-acting opioids in the management of arthritis pain, but the cost-effectiveness of the advantages has not been shown.”¹¹⁹¹

594.6. “The limited study data on effective doses of opioids for OA pain demonstrate efficacy at relatively low doses. Both immediate release and controlled release forms have been effective.”¹¹⁹²

595. The authors of this guideline included several with ties to opioid manufacturers, including Arthur G. Lipman, M.D.,¹¹⁹³ Margaret Caudill-Slosberg, M.D.,¹¹⁹⁴ and April Hazard Vallerand, Ph.D., R.N.¹¹⁹⁵

596. Opioid manufacturers funded the “APS Guidelines Program,” which the APS used to fund its consultants.”¹¹⁹⁶

597. This guideline was used by opioid manufacturers in promoting their opioid products and opioids in general.¹¹⁹⁷

¹¹⁹¹ PKY181215749 at 98.

¹¹⁹² PKY181215749 at 102. When Purdue had concerns about the content of APS materials, it reached out to KOLS involved in the development of the materials to confirm a favorable result for Purdue. For example, when Purdue’s Sally Riddle voiced her worries about the content of the APS Arthritis Guidelines, she communicated these to Harry Lazarus, who then spoke with the chair of the Guidelines, Art Lipman. After speaking with Dr. Lipman, Harry reported back to Sally “I don’t think you will be disappointed with the guidelines.” PPLPC009000006145; *see also* E513_00090393.

¹¹⁹³ Dr. Lipman was a consultant and paid speaker for Endo and Purdue. *See* PKY181215749 at 15.

¹¹⁹⁴ Dr. Caudill-Slosberg was a paid speaker for Purdue. *See* PKY181215749 at 15.

¹¹⁹⁵ Dr. Vallerand was a paid speaker for Purdue and Janssen. *See* PKY181215749 at 15.

¹¹⁹⁶ PKY181215749 at 15.

¹¹⁹⁷ *See, e.g.*, PPLPC012000051510 at 8, PPLPC012000051508, E01_00013311 at 2, PPLP003281201, PPLP012000063578; *see also* APS-MDL00000061 at APS-MDL00000062 (APS Arthritis Guidelines Total Distribution between 2002 and 2007: 193,308); PKY181947933 at 2.

B. American Academy of Pain Medicine

598. According to the mission statement of the American Academy of Pain Medicine (“AAPM”), its purpose is to “provide for quality care to patients suffering with pain, through education and training of physicians, and through the advancement of specialty of Pain Medicine.”¹¹⁹⁸

599. The AAPM received millions of dollars in funding from opioid manufacturers.

599.1. Between 1997 and 2012, Purdue provided more than \$2,000,000.00 in funding to the AAPM,¹¹⁹⁹ and from 2012 and 2017, AAPM received an additional \$700,000.00 from Purdue.¹²⁰⁰

599.2. Between 1997 and 2011, Janssen provided more than \$560,000.00. in funding to the AAP,¹²⁰¹ and from 2012 to 2017, Janssen funded the AAPM with an additional \$83,000.00.¹²⁰²

599.3. From 2010 to 2016, Mallinckrodt provided at least \$239,000.00 in funding to the AAPM.¹²⁰³

¹¹⁹⁸ JAN-MS-00723779.

¹¹⁹⁹ SFC00000001.

¹²⁰⁰ Fueling an Epidemic: Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups. U.S. Senate Homeland Security & Governmental Affairs Committee, Ranking Member’s Office, PPLPC031001561047 at 5. Also available at <https://www.hsgac.senate.gov/imo/media/doc/REPORT-Fueling%20an%20Epidemic-Exposing%20the%20Financial%20Ties%20Between%20Opioid%20Manufacturers%20and%20Third%20Party%20Advocacy%20Groups.pdf>.

¹²⁰¹ JJ-SFC-00000001.

¹²⁰² Fueling an Epidemic: Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups. U.S. Senate Homeland Security & Governmental Affairs Committee, Ranking Member’s Office, PPLPC031001561047 at 5. Also available at <https://www.hsgac.senate.gov/imo/media/doc/REPORT-Fueling%20an%20Epidemic-Exposing%20the%20Financial%20Ties%20Between%20Opioid%20Manufacturers%20and%20Third%20Party%20Advocacy%20Groups.pdf>.

¹²⁰³ CHI_000441993 at 18.

600. As noted in the section above pertaining to the American Pain Society (“APS”), AAPM and APS issued a joint guideline in 1997 that contained misleading statements regarding the safety of opioids.¹²⁰⁴

601. In addition to these guidelines, AAPM provided continuing medical education that was coordinated, at least in part, by opioid manufacturers such as Purdue. For example, an April 2000 email from Purdue’s Robin Hogen described Purdue’s relationship with Dr. Barry Cole, who would later become AAPM’s Executive Director:

[Dr.] Barry [Cole] is now on the road five days a week for Purdue – and seems very happy. He believes he can be more helpful to the Company by remaining a third party – unencumbered by FDA guidelines for what he can say about our products or the class of drugs. By flying under the umbrella of American Academy of Pain Management, he has tremendous credibility and cannot be discounted as a company flak.¹²⁰⁵

602. Similarly, in a May 2001 email exchange involving the AAPM’s Dr. Cole and Purdue’s Dr. Reder, Dr. Cole offered to “provide a written statement for Purdue’s support” and

¹²⁰⁴ AAPM also made misleading statements concerning the risk of addiction in other promotional materials. For example, in a 2005 Question and Answer session with the president of the American Academy of Pain Medicine, Dr. Scott Fishman gave the following misleading statements:

We know that the risks of addiction are there, but they are small and can be managed.... many have argued that if we try in our zeal to minimize the risk to avoid drugs that are addictive, we often wind up using drugs that may be even more toxic, such as NSAIDs or potentially, in some patients, COX-2 inhibitors.

PPLPC0128341 at 3. Likewise, in a 2011 “Interactive Exploration of Integrated Opioid Therapy in Chronic Pain” presentation by AAPM, the following misleading statements were made:

Some long-acting opioids help maintain steady blood serum blood levels, help patients sleep through the night, and eliminate the need for frequent dosing” and that “the less frequent administration may discourage binge behavior in patients with risks for misuse.

MNK-T1_0000984477 at 16.

¹²⁰⁵ PDD8801104393. *See also* PPLPC029000042442 at 2. In this May 2001 email, Dr. Barry Cole wrote the following to Purdue’s Dr. Reder:

Dr. Reder, Thought you’d like to see these items before next weeks meetings in CT.[...] I am attaching some articles and letters from the Cleveland Free Times....all very supportive of OxyContin and calling into question what may be entirely manufactured news. I have spoken with the reporter 3 times. He has asking all of the right questions about the OxyContin “scare.”

Id.

noted that he was “happy to prepare something as an individual or in some official capacity with the American Academy of Pain Management” for the “FDA Advisory Committee meeting in Maryland on June 14/15,” since in Dr. Cole’s opinion “this is all just ‘too much about nothing.’”¹²⁰⁶

C. American Pain Foundation

603. Founded in 1997, the American Pain Foundation (“APF”) described itself as “the nation’s leading independent nonprofit organization serving people with pain.”

604. APF ceased operating in 2012 following congressional questioning about its ties to the pharmaceutical industry, including opioid manufacturers.

605. APF received millions of dollars in funding from opioid manufacturers.

605.1. Between 1999 and 2012, Purdue provided more than \$3,600,000.00 in funding to APF.¹²⁰⁷

605.2. Mallinckrodt contributed a total of \$97,000 in funding to the APF.¹²⁰⁸

605.3. Between 1997 and 2012, Janssen funded APF with more than \$600,000.00.¹²⁰⁹

605.4. Between 1999 and 2012, Endo provided at least \$5,941,671.40 in funding to the APF.¹²¹⁰

¹²⁰⁶ PPLPC029000042442 at 1.

¹²⁰⁷ SFC00000001; *see also* 2001 APF Highlights.((CHI_000406606 at 55) (noting Purdue as its largest funder and also identifying Abbott, Anesta, Bristol-Myers Squibb, Cephalon, Janssen, Knoll, Ligand, McNeil Consumer, Medtronic, Novartis, Ortho-Biotech, Pharmacia, Pfizer, Roxane and Warner Lambert at part of their “broad corporate support.”)

¹²⁰⁸ MNK-T1_0008005740.

¹²⁰⁹ JJ-SFC-00000001.

¹²¹⁰ END00041232 at 8.

606. In exchange for funding APF, opioid manufacturers expected and received inclusion in APF decision making.

606.1. For example, in an August 5, 2000 email from Purdue's Robin Hogen to Dr. David Haddox concerning funding to APF, Hogen stated, "[i]f they want our bucks (and they honestly cannot survive without industry support) they are going to have to learn to live with 'industry' reps on their board. I don't think they can expect huge grants without some say in governance."¹²¹¹

606.2. By at least 2001, APF's Board included members with ties to opioid manufacturers, including Dr. Richard Campbell, a paid consultant for Purdue,¹²¹² and Dr. Richard Portenoy, a paid consultant and speaker for Purdue and Janssen.¹²¹³

607. APF has published promotional materials that contained the same misleading statements regarding the benefits and risks of opioids as those used by opioid manufacturers in their branded promotion.

607.1. In 2000, APF published a "Pain Action Guide" that contained the misleading claim that addiction is rare:

Pain medications rarely cause addiction. Morphine and similar pain medications, called opioids, can be highly effective for certain conditions. Unless you have a history of substance abuse, there is little risk of addiction when these medications are properly prescribed by a doctor and taken as directed. Physical dependence - which is not addiction - may occur as a result of taking these medications if you stop taking these medications suddenly. This usually is not a problem if you go off your medications generally.¹²¹⁴

¹²¹¹ PPLPC025000012558.

¹²¹² PPLP003477687.

¹²¹³ See PKY180772092; ENDO-OPIOID_MDL-01610298; PPLPC020000005715; PDD8801291781; PKY182717470; JAN-MS-00312347.

¹²¹⁴ ABT-MDL-KY-0025968; TEVA_MDL_A_05356629.

607.2. In April 2001, APF issued a news release titled “Balancing News Stories About Opioids,” which again misleadingly claimed addiction to be rare, and further claimed without substantial evidence that opioid medications rarely produce a “high” and allow patients to return to normal lives:

Taking legal, FDA-approved opioid medications as prescribed, under the direction of a physician for pain relief, is safe and effective, and only in rare cases, leads to addiction. When properly used, these medications rarely give a ‘high’ – they give relief. And, most importantly, they allow many people to resume their normal lives.¹²¹⁵

607.3. In 2007, APF provided “messages” to be used in training patient advocates regarding the use of opioids, including the statement that “[p]ain is a national healthcare crises. It is our Nation’s hidden epidemic.” These “messages” also included the following misleading statement regarding addiction:

The public—including doctors and people with pain – often believe that opioid medications are addictive and produce euphoria. The fact is that when properly prescribed by a healthcare professional and taken as directed, these medications give relief – not a ‘high.’¹²¹⁶

607.4. In October 2007, Endo sponsored an APF event “focusing on the vital need for better pain care for members of the military and veterans” entitled “Freedom From Pain: It’s Your Right.”¹²¹⁷ Endo’s financial support for the event included the preparation of a “fact sheet.”¹²¹⁸ The fact sheet included the following statements that downplayed the risk of addiction:

“A number of concerns and misconceptions stand in the way of optimal pain management. These may include fears about”

¹²¹⁵ PKY180302903 at 107.

¹²¹⁶ PPLP004046286 at 2.

¹²¹⁷ ENDO-OPIOID_MDL-02807915 at 3; CHI_000430399.

¹²¹⁸ *Id.* at 2.

“Becoming ‘drugged up’ or addicted to pain medications, if they are prescribed;”¹²¹⁹

*“Unless someone has a past or current history of substance abuse, the chance of addiction is very low when these medications are prescribed by a doctor and taken as directed.”*¹²²⁰

607.5. APF made a similarly misleading statement regarding addiction in the 2009 book titled Exit Wounds – A Survival Guide to Pain Management for Returning Veterans and their Families: “[l]ong experience with opioids shows that people who are not predisposed to addiction are unlikely to become addicted to opioid pain medication.”¹²²¹

607.6. Likewise, in 2011, APF made the following statement regarding addiction in its “Policymaker’s Guide to Understanding Pain & Its Management”:

Under a section titled “some common misconceptions about pain” it was stated that “use of strong pain medication leads to addiction. Many people living with pain, and even some health care practitioners, falsely believe that opioid pain medicines are universally addictive. As with any medication, there are risks, but these risks can be managed when these medicines are properly prescribed and taken as directed.”¹²²²

608. In addition to promoting the misleading claim that opioids are rarely addictive, APF responded to negative media attention related to diversion and abuse of opioids.

608.1. An internal APF presentation highlighted the “Media Frenzy over OxyContin and Other Opioids” and “How APF Has Been Fighting Back.”¹²²³ The presentation highlighted the fact that the APF was involved in “educating the media” by

¹²¹⁹ ENDO-OPIOID_MDL-02807915 at 7.

¹²²⁰ *Id.* at 8.

¹²²¹ SFC00005694 at 107.

¹²²² ENDO-OPIOD_MDL-00654219 at 7.

¹²²³ CHI_000406606 at 42.

“handl[ing] over 125 calls and inquiries from national, state-wide and local media” and “educated journalist on value of opioids while dispelling myths and misconceptions.”¹²²⁴ Further, the APF stated that it had “testified before congress and FDA” and had been “vocal in new pain forum with DEA” where they “insisted on major changes to DEA’s ‘consensus statement.’”¹²²⁵ APF further stated that it “educated professionals” with presentations with titles such as “are pain patients becoming collateral damage in the war on drugs” and “recent federal actions on opioids.”¹²²⁶

608.2. Similarly, the 2001 APF Board of Director Meeting Minutes state that:

[A]s a result of a NY Times article on OxyContin abuse suggesting a link between APF and Purdue Pharma, APF developed a proactive approach to the rise in reports on the negative effects of OxyContin. APF’s media response to queries is that “opioids are one of the most effective ways to treat pain. They offer pain relief, not a ‘high’, when prescribed by a doctor and taken as directed. Opioid-related deaths are the result of ‘drug abuse.’”¹²²⁷

D. Federation of State Medical Boards

609. According to its website, the Federation of State Medical Boards (“FSMB”) is a national non-profit organization representing all 70 state medical and osteopathic boards within the United States and its territories that license and discipline allopathic and osteopathic physicians and, in some jurisdictions, other health care professionals.”¹²²⁸

610. The FSMB received funding from opioid manufacturers.

¹²²⁴ *Id.* at 43.

¹²²⁵ *Id.* at 45.

¹²²⁶ *Id.* at 48.

¹²²⁷ CHI_001260895 at 6.

¹²²⁸ <http://www.fsmb.org/about-fsmb> (last visited Mar. 22, 2019).

610.1. Between 1999 and 2007, Purdue provided at least \$904,742 in funding to the FSMB.¹²²⁹ Purdue's funding paid for copies of the FSMB Pain Model Guidelines and supported the "FSMB National Clearinghouse on Internet Prescribing," the "2003 FSMB Annual Meeting Session," the "Project to Update FSMB Guidelines for the Use of Controlled Substances in the Treatment of Pain," the "FSMB Physician Education Initiative on Safe & Effective Prescribing Practices in Pain Management," and the "distribution of Responsible Opioid Prescribing to [State Medical Boards.]"¹²³⁰

610.2. Between 2000 and 2010, Endo provided at least \$369,025 in funding to the FSMB.¹²³¹ Endo's funding supported distribution of Responsible Opioid prescribing to State Medical Boards and CME Activity related to Opioid REMS.¹²³²

610.3. Teva contributed a total of \$130,000 in funding to the FSMB in donations and as a "grant to support the distribution of Responsible Opioid Prescribing to [State Medical Boards]." ¹²³³

610.4. Mallinckrodt similarly contributed a total of \$100,000 in funding to the FSMB as a "grant to support the distribution Responsible Opioid Prescribing to SMBs." ¹²³⁴

611. As described below, the FSMB has published newsbulletins and guidelines that contained the same misleading statements regarding the benefits and risks of opioids as those used by opioid manufacturers in their branded promotion.

¹²²⁹ SFC00000001.

¹²³⁰ FSMB_00000050 at 11-12.

¹²³¹ ENDO-OR-CID-00754369.

¹²³² FSMB_00000050 at 13.

¹²³³ FSMB_00000050 at 11-12.

¹²³⁴ *Id.*

1. FSMB Model Guidelines for the Use of Controlled Substances for the Treatment of Pain

612. In 1998, the FSMB issued the Model Guidelines for the Use of Controlled Substances for the Treatment of Pain.¹²³⁵

613. These guidelines emphasized that “[i]nadequate pain control may result from physicians’ lack of knowledge about pain management or an inadequate understanding of addiction” while at the same time downplaying the risk of addiction with the false statement that pseudoaddiction is a “[p]attern of drug-seeking behavior of pain patients who are receiving inadequate pain management that can be mistaken for addiction.”¹²³⁶

614. Purdue distributed the Model Guidelines in promotion of its opioids and opioids in general.¹²³⁷

2. Updated FSMB Policy for the Use of Controlled Substances for the Treatment of Pain

615. In 2004, the FSMB issued an update to its Model Policy for the Use of Controlled Substances for the Treatment of Pain, which again contained the following misleading statements regarding addiction: “Notwithstanding progress to date in establishing state pain policies recognizing the legitimate medical uses of opioid analgesics, there is a significant body of evidence suggesting that both acute and chronic pain continue to be undertreated . . . Circumstances that contribute to the prevalence of undertreated pain include . . . ‘misunderstanding of addiction and dependence.’” The Policy then defined pseudoaddiction as the

¹²³⁵ According to a July 23, 2002 letter from Jon A. Sale to Jody Collins, Esq., Assistant Attorney General re: Purdue Pharma, L.P. the Model Guidelines were developed “with the support of the American Academy of Pain Medicine, the American Pain Society, the American Society of Law, Medicine and Ethics, and the University of Wisconsin Pain and Policy Studies Group.” PKY181679246 at 1-2.

¹²³⁶ PPLPC002000136977 at 2.

¹²³⁷ See, e.g., PKY181696752 at 2, PKY181696752 (“Purdue began distributing the Model Guidelines to physicians in early 1999 shortly after they became available. To date, through its field force, Purdue has distributed almost 300,000 copies of the Model Guidelines.”)

“iatrogenic syndrome resulting from the misinterpretation of relief seeking behaviors as though they are drug seeking behaviors that are commonly seen with addiction.”¹²³⁸

616. Opioid manufacturers were involved in drafting this policy update.

616.1. For example, as part of Purdue’s funding of FSMB, Purdue received access to the meeting that “led to the revision of the Model Guidelines to become what is now the [2004] Model Policy, upon which Dr. Fishman’s book [Responsible Opioid Prescribing] is based.”¹²³⁹

616.2. In addition, according to a September 11, 2007 email from David Haddox, he “represented Purdue” at the “meeting that led to the revision of the Model Guidelines to become what is now the [2004] Model Policy” and “many of [his] suggestions and clarifications were accepted by the group [that] revised the Guidelines into the Policy document it is today.”¹²⁴⁰ “In addition, at Dr. Fishman’s request, [Dr. Haddox] performed a detailed review of [the] final draft and submitted the comments to him, many of which” were “accepted.”¹²⁴¹

¹²³⁸ ENDO-OPIOID_MDL-02751850 at 11. The 2004 Model Policy also told healthcare providers that “they should not fear disciplinary action from the Board for ordering, prescribing, dispensing or administering controlled substances, including opioid analgesics, for a legitimate medical purpose and in the course of professional practice . . . [t]he physician’s conduct will be evaluated to a great extent by the outcome of pain treatment, recognizing that some types of pain cannot be completely relieved, and by taking into account whether the drug used is appropriate for the diagnosis, as well as improvement in patient functioning and/or quality of life.” *Id.* at 9.

¹²³⁹ PPLP003477086 at 24.

¹²⁴⁰ *Id.*

¹²⁴¹ *Id.*

617. Members of the the 2004 Model Policy Advisory Council had financial ties to the opioid manufacturers including Dr. David Haddox,¹²⁴² June L. Dahl, Ph.D.,¹²⁴³ and Scott M. Fishman,¹²⁴⁴ M.D.

618. The model policy was used by opioid manufacturers in promoting their opioid products and opioids in general.¹²⁴⁵

3. FSMB Responsible Opioid Prescribing

619. In 2007, the FSMB published Responsible Opioid Prescribing which made the same claims as the 1998 FSMB Model Guidelines and 2004 FSMB Model Policy, including false statements regarding pseudoaddiction.¹²⁴⁶

620. Financial support from Purdue, Endo, Cephalon, and Mallinckrodt in addition to other opioid manufacturers, supported distribution of over 160,000 copies of the book to state medical boards.¹²⁴⁷

621. In addition, Mallinckrodt (and likely others) used Responsible Opioid Prescribing in promotion of its opioids and opioids in general to healthcare providers.¹²⁴⁸

622. In my opinion, opioid manufacturers' support for and involvement with pain advocacy, professional medical and trade group organizations expanded the use of opioids and increased the risk of abuse.

¹²⁴² David Haddox was Vice-President, Risk Management & Health Policy, at Purdue. J. David Haddox Depo. Tr. 57:7-18.

¹²⁴³ See, e.g., PKY180470186.

¹²⁴⁴ See, e.g., SFC00000001; ENDO-OR-CID-00754369 at 21.

¹²⁴⁵ ENDO-OR-CID-00754369 at 13;

¹²⁴⁶ ENDO-OR-CID-00754369 at 13.

¹²⁴⁷ FSMB000000050 at 10-14, 18-19.

¹²⁴⁸ MNK-T1_0000098925 (Mallinckrodt).

XII. CORRECTIVE MEASURES

623. Based on the totality of the above, it is my opinion that corrective promotion, advertising, and professional education initiatives to audiences that received the false and misleading messages discussed in this report are called for. Though not intended as an exhaustive list, examples of such corrective promotion and advertising could include the following messages:

501.1 Opioids present an unavoidable risk of addiction, overdose and death, even when used as prescribed.

501.2 Opioids should not commonly be used for chronic pain.

501.3 Opioids should be prescribed at the lowest possible dose for the shortest possible time.

624. Additional messages such as those adopted by the Truth Initiative should be used in corrective promotion.

625. In addition to corrective promotion, manufacturers should assure that no claims, including any superiority claims, about opioids are made without validation of those claims by high-quality and well-controlled clinical studies.

626. Moreover, to correct the results of past practices, in my opinion, manufacturers should not fund treatment guidelines, organizations that issue treatment guidelines, or any authors of guidelines that concern pain, opioids or addiction. Disclosure of past and present funding from manufacturers to organizations and individuals that issue or author treatment guidelines should also be made.

627. As in other corrective programs, it would also be useful to disclose historical manufacturer documents concerning opioids to the public, while still protecting personal health information.

XIII. CONCLUSIONS

1. In this report, I have provided the following opinions:
2. In my opinion, Purdue utilized promotional tactics that misbranded OxyContin as a drug that is safer and more effective than it actually is without substantial evidence.
3. In my opinion, Purdue's marketing minimized the similarities between OxyContin and morphine.
4. In my opinion, Purdue falsely marketed OxyContin as having a lower potential for abuse as compared to other opioid products.
5. In my opinion, Purdue's marketing misleadingly claimed without substantial evidence that OxyContin was less addictive than competitor opioid products.
6. In my opinion, Purdue misleadingly told health care providers that patients exhibiting signs of addiction were likely "psuedoaddicted" and in need of additional opioids to treat pain.
7. In my opinion, Purdue minimized the risks of tolerance and physical dependence that patients could experience with OxyContin.
8. In my opinion, Purdue's marketing minimized the risks of respiratory depression, addiction, and abuse associated with higher doses of OxyContin.
9. In my opinion, Purdue overstated the 12-hour analgesic benefit of OxyContin.
10. In my opinion, Purdue overstated the benefits of OxyContin with respect to sleep, work, and physical activity/leisure.
11. In my opinion, Purdue put patients at risk by developing a strategy to increase the total daily OxyContin dose without informing the public that OxyContin was not effective for 12 hours.

12. In my opinion, Purdue promoted OxyContin for indications that were broader than supported by substantial evidence and for which safety and efficacy were not established.

13. In my opinion, Purdue failed to align its promotional activities with its Risk Management Program and Risk Evaluation and Mitigation Strategies.

14. In my opinion, Endo's marketing activities understated the risks of the entire class of opioids.

15. In my opinion, by promoting higher doses of Percocet, Endo minimized the risks of respiratory depression and abuse associated with higher doses of opioids.

16. In my opinion, Endo overstated the benefits of Percocet with respect to quality of life.

17. In my opinion, Endo falsely marketed Opana ER as having lower abuse potential and as safer than other opioid products.

18. In my opinion, Endo minimized the risk of addiction associated with Opana ER and funded various pain organizations to likewise minimize the risk of addiction.

19. In my opinion, Endo falsely told healthcare providers that patients exhibiting signs of addiction could be exhibiting "pseudoaddiction" and in need of additional opioids to treat pain.

20. In my opinion, Endo promoted Opana ER as having no dose ceiling but minimized the risks associated with higher doses.

21. In my opinion, Endo overstated the benefits of Opana ER with respect to work and functionality.

22. In my opinion, Endo minimized the risk of addiction associated with Opana ER and opioids in general through its distribution of the AAPM/APS "Consensus Statement on the

Use of Opioids for the Treatment of Chronic Pain” and “A clinical guide to Opioid Analgesia” as part of the Opana ER Riskmap.

23. In my opinion, the “Professional Education Initiatives” Endo supported in the Opana ER Riskmap minimized the risk of addiction associated with opioids.

24. In my opinion, Endo marketed Opana ER as “Crush Resistant” despite FDA’s instruction otherwise.

25. In my opinion, Endo failed to take reasonable steps to protect the public health despite increasing evidence of Opana ER Reformulated abuse.

26. In my opinion, Janssen’s marketing of Duragesic broadened its indications beyond the label, and thereby expanded the use of long acting opioids and contributed to the change in the practice of medicine.

27. In my opinion, Janssen misleadingly promoted Duragesic as superior to oral opioids, especially OxyContin, without substantial evidence, and overstated its functionality benefits.

28. In my opinion, Janssen misleadingly promoted Duragesic as having no or lower abuse potential, particularly compared with OxyContin, without substantial evidence.

29. In my opinion, Janssen made misleading, unsubstantiated and shifting claims regarding the abuse potential of the reservoir v. matrix formulations of Duragesic as the sales and regulatory environment changed.

30. In my opinion, Janssen’s promotion of Duragesic understated its risks and overstated its benefits, and was false and misleading.

31. In my opinion, Janssen overstated the benefits of Nucynta’s mechanism of action, promoting it as offering increased efficacy without substantial evidence.

32. In my opinion, Janssen overstated the benefits of Nucynta's GI tolerability, making superiority claims without substantial supporting evidence.

33. In my opinion, Janssen's promotion of Nucynta misleadingly minimized the risks of abuse and addiction.

34. In my opinion, Teva marketed Actiq for indications that lacked substantial evidence to support safety.

35. In my opinion, Teva failed to comply with its risk management strategies in marketing Actiq.

36. In my opinion, Teva promoted Fentora for non-malignant pain, for which it lacked substantial evidence to support safety.

37. In my opinion, Actavis promoted Kadian for indications broader than supported by substantial evidence and for which safety and efficacy were not established.

38. In my opinion, Actavis's promotional materials overstated the benefits of Kadian with respect to patient functionality and quality of life

39. In my opinion, Actavis falsely marketed Kadian as safer and more effective than other opioid products.

40. In my opinion, Actavis falsely promoted Kadian as having no alcohol-induced dose-dumping effect and failed to take reasonable measures to correct prescriber misperceptions regarding this promotional claim.

41. In my opinion, Actavis's promotion of opioids minimized the risks of addiction and abuse.

42. In my opinion, Mallinckrodt falsely promoted Exalgo as safer than other opioid products.

43. In my opinion, Mallinckrodt's sales training misleadingly minimized the risks associated with higher doses of opioids and encouraged sales representatives to make misleading claims regarding abuse deterrence.

44. In my opinion, Mallinckrodt misleadingly minimized the risk of addiction and funded the CARES Alliance which likewise understated the risk of addiction.

45. In my opinion, Mallinckrodt misleadingly told healthcare providers and trained its sales force that patients exhibiting signs of addiction were likely "pseudoaddicted" and in need of additional opioids to treat pain.

46. In my opinion, Mallinckrodt falsely marketed Xartemis as having a lower potential for abuse as compared to other opioid products.

47. In my opinion, through the pain advocacy group guidelines and materials they helped develop and disseminate, opioid manufacturers contributed to altering the standard of care for the treatment of pain by encouraging healthcare providers to view pain as a "fifth vital sign" that demanded aggressive treatment with opioids.

48. In my opinion, opioid manufacturers' support for and involvement with pain advocacy, professional medical and trade group organizations expanded the use of opioids and increased the risk of abuse.

49. In my opinion, the promotional violations discussed above endanger public health because they encourage the use of opioids in circumstances other than those in which the drugs have been approved, overstate their benefits and minimize their risks.

50. In my opinion, because the promotional violations discussed in this report are serious, corrective promotion and medical education that disseminates truthful, non-misleading,

and complete corrective messaging about the violations discussed above to the audiences that received the violative promotion is warranted.

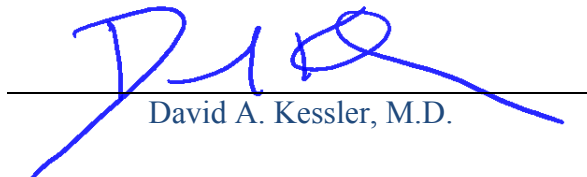
51. In my opinion, the need for corrective promotion here is supported by research that has demonstrated that similar corrective promotion can be effective in countering false and misleading statements made about prescription drug products.

52. In my opinion, manufacturers should assure that no claims, including any superiority claims, about opioids are made without validation of those claims by high quality and well controlled clinical studies.

53. In my opinion, to correct the results of past practices, manufacturers should not fund treatment guidelines, organizations that issue treatment guidelines, or any authors of guidelines that concern pain, opioids or addiction. Disclosure of past and present funding from manufacturers to organizations and individuals that issue or author treatment guidelines should also be made.

54. Based on the totality of the above, it is my opinion that the manufacturers' departures from FDA standards would be expected to (and likely did) have an affect on how healthcare providers prescribed opioids, contributing to a shift in the practice of medicine with regards to the use of opioids in the treatment of pain. This change in the practice of medicine led to an increase in opioid prescriptions, an increase of opioids in interstate commerce, and an increase in inappropriate use of opioids, all of which in turn increased the risk of opioid abuse and contributed to a public health crisis.

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